Published in final edited form as:

J Affect Disord. 2018 January 01; 225: 129–136. doi:10.1016/j.jad.2017.08.027.

Considering sex differences clarifies the effects of depression on facial emotion processing during fMRI

L. M. Jenkins¹, A.D. Kendall^{1,2}, M. T. Kassel¹, V. G. Patrón¹, J. R. Gowins¹, C. Dion¹, S. A. Shankman^{1,3}, S. L. Weisenbach^{1,4}, P. Maki¹, and S. A. Langenecker^{1,5,*}

¹Department of Psychiatry, The University of Illinois at Chicago

²Department of Psychology, Northwestern University

³Department of Psychology, The University of Illinois at Chicago

⁴Department of Psychiatry, The University of Utah

⁵Departments of Psychiatry, The University of Michigan

Abstract

Background—Sex differences in emotion processing may play a role in women's increased risk for Major Depressive Disorder (MDD). However, studies of sex differences in brain mechanisms involved in emotion processing in MDD (or interactions of sex and diagnosis) are sparse.

Methods—We conducted an event-related fMRI study examining the interactive and distinct effects of sex and MDD on neural activity during a facial emotion perception task. To minimize effects of current affective state and cumulative disease burden, we studied participants with remitted MDD (rMDD) who were early in the course of the illness. In total, 88 individuals aged 18 to 23 participated, including 48 with rMDD (32 female) and 40 healthy controls (HC; 25 female).

Results—fMRI revealed an interaction between sex and diagnosis for sad and neutral facial expressions in the superior frontal gyrus and left middle temporal gyrus. Results also revealed an interaction of sex with diagnosis in the amygdala.

*Correspondence to Scott A. Langenecker, Cognitive Neuroscience Center, Department of Psychiatry, The University of Illinois at Chicago, 1601 W Taylor St. Chicago, IL 60612 and slangen@uic.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

Lisanne Jenkins preprocessed the data, built fMRI models, conducted the data analyses, researched the literature and was the main writer of the manuscript. *Ashley Kendall* researched the literature and wrote parts of the manuscript. *Michelle Kassel* collected and preprocessed the data, built fMRI models, and revised the manuscript. *Victor Patron* built fMRI models, researched the literature and wrote parts of the manuscript. *Jennifer Gowins* preprocessed the data, built fMRI models, and revised the manuscript. *Catherine Dion* preprocessed the data, built fMRI models, and revised the manuscript. *Stewart Shankman* provided guidance on study design and analysis, and reporting of results, and revised the manuscript. *Sara Weisenbach* researched the literature and provided guidance on the reporting of results, and revised the manuscript. *Pauline Maki* provided guidance on study design and analysis, and the reporting of results, and revised the manuscript. *Scott Langenecker* conceived of the study, obtained the funding that paid for it, oversaw data collection, preprocessing and analysis, and revised the manuscript. All authors have approved the final article.

There are no conflicts of interest.

Limitations—Data was from two sites, which might increase variability, but it also increases power to examine sex by diagnosis interactions.

Conclusions—This study demonstrates the importance of taking sex differences into account when examining potential trait (or scar) mechanisms that could be useful in identifying individuals at-risk for MDD as well as for evaluating potential therapeutic innovations.

Keywords

sex differences; facial emotion perception; major depression; remitted; fMRI; superior frontal gyrus

1. Introduction

Facial emotion perception is a fundamental element of social functioning that facilitates individuals' abilities to evaluate and respond to the reactions of others, build and strengthen interpersonal relationships and navigate social networks (Russell, Bachorowski, & Fernandez-Dols, 2003). As such, difficulties in facial emotion perception might limit the extent and benefits of social support systems. Individuals with Major Depressive Disorder (MDD) have exhibited processing biases of emotional material, including facial expressions (see Mathews & MacLeod, 2005). These biases are generally away from positive and/or toward negative facial expressions (e.g., Hale, 1998; Joormann & Gotlib, 2007; Leyman, De Raedt, Schacht, & Koster, 2006; Surguladze et al., 2004). Findings of biases in emotion perception in MDD support interpersonal models of MDD, which highlight the importance of social skills deficits and biases in the etiology and maintenance of MDD. It has been suggested, for example, that the tendency of depressed individuals to be biased toward negative social cues contributes to their feelings of decreased social support and thereby exacerbates depressive symptoms (Gotlib & Hammen, 1992). These findings also converge with Beck's classic (1967) cognitive model of depression, which places biased processing of emotional information at the core of MDD. Notably, Beck holds that such biases are not only state markers of active MDD (aMDD), but also underlying trait vulnerabilities for MDD onset and recurrence.

MDD is highly prevalent (Kessler et al., 2005) and recurrent; an estimated half to two-thirds of individuals who experience a major depressive episode will have at least one more over the course of their lives (Kessler, 2002). Elucidating state and trait risk factors for MDD, such as those associated with impaired emotion perception, could aid in identifying individuals at greater risk for onset and relapse, and potentially lead to earlier interventions. The present study therefore sought to identify performance and neurobiological intermediate phenotypes of MDD whilst minimizing the potential confounding effects of active symptoms by studying individuals with remitted MDD (rMDD) in late adolescence and early adulthood. This approach offers a unique opportunity for determining whether behaviours such as biased facial emotion processing are a trait risk marker for MDD, instead of potentially reflecting state experiences of current depression. Although we cannot completely rule out 'scar' effects of chronic illness burden, we can limit their influence by restricting the sample to those who have experienced few depressive episodes. Further, by

restricting the age range of participants to young adults in the study we can also minimize developmental, disease progression, and age/degenerative effects.

Most studies on facial emotion perception have been conducted in aMDD. However, there is some evidence that response to positive facial cues may be especially important in distinguishing individuals with rMDD from those who have never been clinically depressed. For example, participants with rMDD have been shown to require greater intensity of emotional expression to identify happy faces compared to never-depressed controls (LeMoult, Joormann, Sherdell, Wright, & Gotlib, 2009). Healthy controls (HCs) have also demonstrated a bias towards positive facial expressions and away from negative facial expressions in an attention bias (i.e. dot probe) task, whereas currently and formerly depressed participants showed no such bias (Joormann & Gotlib, 2007). Still other studies have shown that individuals with rMDD have similar accuracy as HCs (Jenkins et al., 2016), unlike those with aMDD (e.g., Kohler, Hoffman, Eastman, Healey, & Moberg, 2011; Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996).

Studies using functional magnetic resonance imaging (fMRI) have revealed neural differences during facial emotion processing in rMDD. Two general, and sometimes contradictory, patterns of findings have emerged. First, there is evidence of increased neural activity in response to emotional faces among individuals with rMDD compared with HCs. This has included increased activity in the bilateral middle temporal gyrus and left superior frontal gyrus for blocks of emotional faces compared to animals (Jenkins et al., 2016), as well as increased activity in the bilateral dorsolateral prefrontal cortex (DLPFC) and right caudate for blocks of fearful faces (Norbury, Selvaraj, Taylor, Harmer, & Cowen, 2010). Increased activity in the remitted state has also been reported in the amygdala in response to masked sad minus neutral and masked happy minus neutral faces (Victor, Furey, Fromm, Ohman, & Drevets, 2010) and unmasked sad faces (Neumeister et al., 2006) during implicit emotion tasks as well as during explicit classification of emotional faces compared to animals (Jenkins et al., 2016). Notably, other studies have shown that amygdala hyperactivation normalizes with antidepressant treatment (Arnone et al., 2012; Sheline et al., 2001). It remains unclear whether this normalization is a byproduct of antidepressant use or a remission effect.

The second pattern of imaging findings is of decreased activation in response to specific emotional faces among individuals with rMDD versus HCs, typically after subtracting BOLD signal in response to neutral faces. For example, studies have reported reduced activation in the left ventral striatum in response to sad faces (Neumeister et al., 2006), right insula, fusiform gyrus, putamen and bilateral hippocampus in response to sad minus neutral faces and in the left hippocampus and BA44 in response to fearful minus neutral faces (Thomas et al., 2011) and the left orbitofrontal cortex (OFC) and bilateral DLPFC in response to fearful minus neutral faces (Kerestes et al., 2012). A recent meta-analysis of MDD studies highlighted the severe lack of convergence across neuroimaging experiments, even across meta-analytic findings (Müller et al., 2017). The authors noted that this ‘perplexing’ divergence could be due to analytic factors such as use of uncorrected inference procedures, methodological differences, and heterogeneous clinical populations. For example, methodological factors could include whether neutral or happy faces are used for

the contrast (Kerestes et al., 2012; Norbury et al., 2010), and the type and duration of treatment participants have experienced contributes to clinical heterogeneity. This in turn could impact activation in the DLPFC during implicit negative facial emotion processing (Fales et al., 2009; Fu et al., 2004). Another crucial variable to consider that could potentially be responsible for inconsistencies in results is sex. While many studies attempt to collect both male and female participants, too often sex is neglected as a variable of interest, and studies of its interaction with history of depression are completely lacking. It is particularly important to consider the interaction of sex and history of depression given that females are twice as likely as males to experience a depressive disorder (e.g., Wade, Cairney, & Pevalin, 2002). Sex could therefore be another key factor contributing to and/or obscuring the literature on facial emotion perception.

Biases in facial emotion processing could be a potential mechanism leading to sex differences in MDD, given that research consistently shows between-sex behavioural and neural differences in this domain (Stevens & Hamann, 2012; S.L. Weisenbach et al., 2014; Whittle, Yucel, Yap, & Allen, 2011; Wright et al., 2009). In general, females are more accurate than males at identifying facial emotions, particularly negative ones (Montagne, Kessels, Frigerio, de Haan, & Perrett, 2005; Schienle, Schafer, Stark, Walter, & Vaitl, 2005). Neuroimaging studies have also shown that females recruit different brain regions compared to males during facial emotion processing (S. L. Weisenbach et al., 2014; Whittle et al., 2011). In a meta-analysis of neuroimaging studies, Stevens and Hamann (2012) found that the left amygdala showed greater activation for negative emotions in females and for positive emotions in males. A recent study by our group with a separate sample reported an interaction between aMDD (vs HC), age (younger vs. older) and sex in several regions, using a block design (Briceño et al., 2015). Notably, these included the DLPFC, inferior and superior frontal gyri, and cingulate, with hyperactivation in these regions for young females with aMDD and hypoactivation in young males with aMDD compared to their same sex HC counterparts.

What is intriguing in light of prior research is the seeming discrepancy between the increased risk for MDD in females, who are typically *more accurate* at emotion processing than males, while those with MDD typically exhibit *worse* emotion processing abilities than HCs. To date, research has been inconclusive on why emotion processing strengths and weaknesses may emerge/present differentially in males and females. Primarily, based on a recent finding from a study of aMDD (Briceño et al., 2015), we hypothesized an interaction between sex and diagnosis in a young rMDD sample (a trait hypothesis), as to our knowledge no previous study has sought to examine sex differences in neural activity during facial emotion processing in individuals with rMDD compared to HCs. Specifically, we predicted that males with rMDD would show hypoactivity compared to females with rMDD in emotion processing regions, and that male HCs would show hyperactivity compared to female HCs in these regions.

To our knowledge, no fMRI studies of rMDD have examined explicit facial emotion perception in an event-related design. The present study is not only the first to do so, but is also the first to examine the interaction of Sex with diagnosis in this population.

2. Materials and Methods

2.1. Participants

The study included 105 individuals aged 18–23 years. The rMDD group comprised 58 (40 female) individuals with a history of MDD (1–3 prior episodes¹) who were in remission at the time of the study, as defined by DSM-IV-TR criteria. The mean number of years well was 2.98 (SD=1.73). The HC group contained 46 participants (30 female). Participants were recruited from two urban communities: Ann Arbor, Michigan, and Illinois, Chicago, and tested at two sites: the University of Michigan (UM, N=35, 16 HC) and the University of Illinois at Chicago (UIC, N=70, 30 HC). The sample of participants for this study overlaps by 84 participants (95.5%) with a previously reported block design analysis of the study (Jenkins et al., 2016) that examined general reactivity to faces minus a control condition of animals in individuals with rMDD compared to HCs. Notably, the present study is distinct in its analysis approach as it conducted an event-related analysis of specific emotions: Happiness, Anger, Fear, Sadness and Neutral, rather than a block design analysis of faces contrasted with non-faces (animals). Furthermore, this work tests the interaction between sex and diagnosis. Finally, this study included assessments of stability of diagnostic, sex, and interactive effects - with time 2 measurements that were completed 4–12 weeks later (see Supplement).

The Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) was given to ascertain diagnosis (and remission from active MDD) and was confirmed with parent/guardian interview using a modified Family Interview for Genetic Studies (Maxwell, 1992) or treatment records. Three HC and four rMDD participants were left-handed. Exclusion criteria included substance abuse or dependence within the previous year, psychoactive medication (other than psychostimulant) use within the past 30 days, regular smoking, suicide attempt/hospitalization within the past six months, any neurological condition, personal or family history of psychosis.

Individuals with movement greater than 1.5 mm or uncorrected artifacts (after preprocessing, see methods below) in more than 33% of their fMRI data were removed from the sample, resulting in a final sample size of 88 (61 from UIC). Table 1 reports the number of males and females in each final group, and the demographic characteristics, estimated verbal IQ (VIQ) and HDRS. ANOVAs were used to examine potential age and group differences and interactions in these variables.

2.2. Measures

2.2.1. Facial Emotion Perception Test (FEPT)—The Facial Emotion Perception Test (Langenecker et al., 2005; Langenecker et al., 2007; Rapport, Friedman, Tzelepis, & Van Voorhis, 2002) has been used in fMRI studies of aMDD to assess emotion perception and processing (Briceño et al., 2013). This task rapidly presents colour faces from the MacBrain Foundation set (Tottenham et al., 2009) that participants categorize by emotion. Each trial begins with a fixation cross presented for 500ms, followed by a face expressing either

¹Median=1. However, one person with 4 prior episodes, two people with five episodes and one with six prior episodes were included with recurrences to the illness that included seasonal affective components.

Anger, Happiness, Sadness, Fear or *Neutral* emotion for 300ms, followed by a visual grey-scale mask for 100ms to prevent visual afterburn phenomena (See Supplement for a task diagram). Participants responded in the 3100ms following the face using a 5-button response ‘claw’ (Psychology Software Tools). In addition to Neutral faces, the task includes a second control condition (not analyzed in the present study) in which participants identify animals (primates, cats, dogs, fish and birds) to control for activity related to visual processing, praxis, response selection and execution. Blocks of Faces and Animals were interspersed with rest blocks across five runs of 4 minutes, 20 seconds each.

2.3. Procedures

Written informed consent was obtained according to the guidelines of the Institutional Review Boards of UM and UIC and consistent with the Declaration of Helsinki (BMJ 1991; 302: 1194). Participants were compensated for their involvement.

Participants completed a practice trial of the FEPT prior to fMRI scanning. The FEPT was completed during the second half of a 90-minute fMRI session. Other tasks were completed earlier in the scanning session, to be reported elsewhere.

2.3.1. MRI acquisition—Whole-brain imaging was performed at two sites, both with a 3T GE scanner: a Signa (release VH3, General Electric, USA) at UM used a reverse spiral sequence to acquire 36 slices, 3.5mm thick; a 3T GE MR750 scanner at UIC used a gradient-echo axial echo-planar imaging sequence to acquire 44 slices, 3mm thick. Further details are reported in the Supplement. Site was included as a covariate in all analyses.

2.3.2. MRI processing—UM data were despiked using FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) by the UM fMRI laboratory prior to transfer to UIC. Data from UIC were despiked using AFNI (<http://afni.nimh.nih.gov/afni/>). All data were then slice-time corrected in SPM (<http://www.fil.ion.ucl.ac.uk/spm/>) and realigned to the 10th volume in FSL using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). Brain extraction of anatomical images was performed with FSL’s Brain Extraction Tool (Smith, 2002) then co-registered to functional images and spatially normalized to Montreal Neurological Institute (MNI) space in SPM, with a final reconstructed spatial resolution of $2 \times 2 \times 2$ mm. Smoothing was completed in SPM with a full-width at half-maximum filter of 5mm. First level models were created in SPM8, and included the motion regressors of translation in x, y and z planes. A high pass filter of 128 seconds and a whole brain explicit mask were also utilized. Time series data were convolved with the hemodynamic response function. Second level models were also built in SPM8.

2.3.3. Statistical analysis—Behavioural data were missing for 10 people (4 HC, 6 rMDD) due to technical error, so for the analysis of behavioural performance, these participants were excluded, and for the neuroimaging analyses, we substituted the mean behavioural data of their diagnostic and sex group. A MANCOVA was calculated with Diagnosis and Sex as independent variables, Site as a covariate, and Accuracy for Anger, Fear, Happiness, Sadness and Neutral as five dependent variables.

For the neuroimaging data, five second-level ANCOVAs were calculated, one for each emotion (Anger, Happiness, Sadness, Fear or Neutral), with Diagnosis and Sex as independent variables, and Site and Accuracy for that specific emotion as covariates. 3dClustSim was used to generate a Monte Carlo threshold for significance that combines height and extent of activation, here a $p < .005$ and $k > 58$ ($p < .01$ whole brain corrected for each model within SPM (Eklund, Nichols, & Knutsson, 2016)). Correcting for multiple comparisons, these results have a Family Wise Error rate of ($p < .01 * 5$ (emotions)) = $p < .05$). Post hoc analyses of the interaction between Sex and Diagnosis were conducted in SPSS with data extracted from any significant clusters from the second-level fMRI ANCOVA, to illustrate the directions of activation for each subgroup within the interaction.

The results of these analyses are reported in the final column of Table 2.

As we had obtained a second scan in a subset of participants from UIC (N=52, 22 HC and 30 rMDD, 17 Male and 35 Female), we were able to evaluate stability of fMRI effects over time. The inter-scan interval ranged from 17 to 137 days ($M = 49$, $SD = 21$), and did not differ significantly between Diagnostic groups, $t(50) = -0.56$, $p = .58$, or Sexes $t(50) = -0.53$, $p = .60$. These results, including intra-class correlation coefficients (ICC) to test the stability of effects over time, are presented in the Supplement.

2.3.4. ROI analysis—To investigate group differences in the amygdala, we created a bilateral amygdala mask using WFU pickatlas with a dilation of 1. We then applied this mask to each emotion contrast, using a reduced threshold of at $p = .05$, $k = 15$. Follow-up analyses investigated hemispheric differences and the direction of any observed effects. We created separate left and right hemisphere ROIs from the above described mask, then extracted signal from each individual's first level model from the Anger, Fear, Happy, Sad and Neutral contrasts. We calculated a repeated measures ANCOVA with Hemisphere and Emotion (Anger, Fear, Happy, Sad, Neutral) as within-subject factors, Diagnosis and Sex as independent variables, and Accuracy for each emotion and Site as covariates. An additional ROI analysis of the subgenual anterior cingulate cortex is presented in the Supplement.

3. Results

3.1. Performance results

For behaviour accuracy, there was no significant main effect of Diagnosis, $F(5, 66) = 1.36$, $p = .251$, $\eta^2_p = .09$, no significant main effect of Sex, $F(5, 66) = 1.36$, $p = .250$, $\eta^2_p = .09$, and no significant Diagnosis by Sex interaction, $F(5, 66) = 1.52$, $p = .197$, $\eta^2_p = .10$. However, there was a significant effect of the covariate Site, $F(5, 66) = 2.64$, $p = .031$, $\eta^2_p = .17$, with participants from UM performing better than those from UIC. Due to site differences in Accuracy, we included Site as a covariate in all fMRI analyses. Accuracy values for each emotion are reported in the Supplement.

3.2. Neuroimaging results

3.2.1. Interaction of Diagnosis by Sex—There was a significant interaction of Diagnosis and Sex for the Sad and Neutral contrasts (Figure 1, Table 2). Post hoc analyses examined the interaction of Sex and Diagnosis group. For the Neutral contrast, Male HCs

displayed significantly greater activity than Female HCs and Males with rMDD showed significantly less activity than Females with rMDD in the right thalamic cluster. This pattern was also observed in the Sad contrast, in the right superior frontal gyrus (SFG) cluster. However, in the left middle temporal gyrus and bilateral midbrain during the Sad contrast, the opposite pattern was seen, with Male HCs demonstrating significantly less activity than Female HCs and Males with rMDD showing greater activity than Females with rMDD.

3.2.2. rMDD only Sex sub-analysis—Finally, we were interested in examining the effect of Sex in the rMDD group only. There was a main effect of Sex for all emotions and Neutral, with Females demonstrating greater activity than Males in all analyses. Figure 2 shows the overlap of significant activity for all contrasts, with the most overlap evident in the left precentral and the right superior frontal gyri.

3.2.3. Amygdala ROI analysis—Figure 3 shows a significant interaction of Diagnosis and Sex for the Sad contrast in the left amygdala.

Post hoc analyses found a significant three-way interaction between Emotion, Hemisphere, and Sex, $F(3.73, 286.86, \text{Huynh-Feldt corrected}) = 2.51, p = .046, \eta^2_p = .03$. We therefore conducted separate repeated measures ANCOVAs for each emotion, removing accuracy for the non-modeled emotions from the covariates. There was no significant interaction of Diagnosis and Sex for Anger, Fear, Happy, Sad or Neutral contrasts. For the Sad contrast, there was a significant Hemisphere by Sex interaction, $F(1, 81) = 4.17, p = .044, \eta^2_p = .05$, but separate repeated measures ANCOVAs for each Sex for Sadness found there was no significant effect of Hemisphere for Males or Females. Figure 4 shows the estimated marginal means from the left and right amygdala for each Diagnosis, Sex and Hemisphere, with covariates Sad accuracy and Site.

4. Discussion

The present study illustrates the complexity of studying the neural systems underlying facial emotion perception in mood disorders, as there were significant interactions between Diagnostic group and Sex. This was demonstrated in blood oxygen level-dependent (BOLD) fMRI activity during perception of Sad and of Neutral expressions. As hypothesized, the general pattern was of Females with rMDD demonstrating hyperactivity compared to Males with rMDD, whereas Males HCs showed hyperactivity compared with Female HCs, particularly in right superior frontal gyrus (sad faces) and right dorsomedial nucleus of the thalamus (neutral faces). These findings are interpreted below in light of prior research, however due to the scarce corpus of data addressing Diagnosis by Sex interactions, in some instances we can only comment on these results in relation to prior work on Diagnostic or Sex differences alone.

4.1.1 fMRI Sex by Diagnosis interaction

The strongest support for the hypothesized interaction between Diagnosis and Sex, in which Male HCs showed greater activity than Female HCs and Males with rMDD showed lesser activity than Females with rMDD, was found in the right superior frontal gyrus (SFG) during Sad facial expressions, and the right dorsomedial thalamus during Neutral

expressions. There were also interaction effects in the opposite of the hypothesised direction for Sadness in bilateral parahippocampal gyrus and midbrain, as well as left anterior middle temporal gyrus. Using the Faces minus Animals contrast of the FEPT, Briceño et al. (2015) also found in their sample of young adults that Males with aMDD showed less activity than Females with aMDD in the right SFG, although the SFG cluster in BA6 in the present study was superior to the SFG cluster in BA9 observed by Briceño et al. Previous research has also documented an interaction of MDD diagnosis and sex in resting state activity in the SFG (Yao et al., 2014), as males with MDD showed reduced amplitude of low frequency fluctuations (ALFF, an index of spontaneous brain activity) compared to females with MDD. A separate study found that ALFF within and resting state connectivity of the medial part of the left SFG was significantly negatively correlated with the efficiency of executive control processing (Xu et al., 2014). Indeed, the SFG is involved in working memory (du Boisgueheneuc et al., 2006) and attention (Corbetta, Patel, & Shulman, 2008; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The SFG is important for emotion regulation (Ochsner & Gross, 2005), particularly inhibition of negative affect (Phan et al., 2005), including via the cognitive strategy of reappraisal which involves altering the emotional interpretation of a stimulus (Kalisch, 2009), attentional modulation (Klumpp, Angstadt, & Phan, 2012), and distraction (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011). Patients with rMDD are reportedly impaired at using reappraisal to regulate emotions and show increased activity compared to controls in the dorsomedial PFC during emotion regulation via distraction (Kanske, Heissler, Schonfelder, & Wessa, 2012).

There was a significant interaction of Diagnosis and Sex in the left amygdala. Whilst not significant, Figure 4 showed that male HCs showed less left amygdala activity than males with rMDD, and female HCs showed more left amygdala activity than females with rMDD. This pattern was inverse to that of the main results. A recent meta-analysis of neuroimaging studies (Miller, Hamilton, Sacchet, & Gotlib, 2015), found that the left amygdala was more active in youth with MDD compared to HCs, however the effect of Sex or its interaction with Diagnosis was not examined. Future studies that examine these interactions are required to replicate this finding.

Our finding of activation of the SFG, an area important for emotion regulation, highlights an important point. While the present task was an explicit emotion identification task, it is possible that emotion regulation was also initiated. Therefore, our observed interaction between Sex and Diagnosis in the SFG could be related to sex and diagnostic differences in functional activation during emotion regulation, and the corresponding neuroanatomical differences underlying these functions. Indeed, in our sub-analysis of Sex differences in rMDD only, we observed significant activity in the right SFG for all contrasts, with Females showing greater activity than Males. Females with rMDD may be over-regulating emotion and/or less efficient, possibly given the prior experience of an inability to do so during the active depressed state. Thus the recruitment of the emotion regulation region of the SFG (in addition to the precentral gyrus) may reflect compensatory neural activity in order to achieve equivalent performance. Sex differences in emotion regulation may be associated with increased levels of and reactivity to stress in Females compared with Males (Hankin & Abramson, 2001) and increased prevalence of MDD in Females. Our findings extend those of Briceño et al. (2015) to confirm the importance of sex differences in emotion perception

and their interaction with depression history even in individuals who are currently well, and suggest that they may represent trait markers present in MDD, regardless of active or remission status.

In light of the above findings, the presence of hypoactivation in response to facial expressions of several emotions in rMDD, absent the active disease symptoms, combined with evidence presented in the Supplement of stability of these findings over time, suggests a possible intermediate phenotype (Gottesman & Gould, 2003; Langenecker, Saunders, Kade, Ransom, & McInnis, 2010). Emotion processing is a complicated intermediate phenotype, as some aspects of dysfunction differ between active and remitted disease states (e.g. accuracy, amygdala activation), whereas others show clearer differences. Studies of young at-risk individuals who have not experienced MDD could support that reduced neural processing of emotional faces is indeed an intermediate phenotype.

4.3. Limitations

The primary limitation of this study was that it was conducted over two sites using different imaging sequences, albeit by the same investigative team, using an identical protocol and similar scanner types. To avoid potential confounding influence of Site, we included it as a covariate in the analyses, and also evaluated each effect (e.g., Sex, Sex by Diagnosis) for any undue influence of one Site or another. Combining data from two sites was necessary in order to obtain enough males for the rMDD group, giving us an advantage over previous studies that were not sufficiently powered to examine Sex by Diagnosis interaction. To illustrate, Kerestes et al. (2012) reported four males with rMDD, Thomas et al. (2011) and Norbury et al. (2010) each reported seven, and in the largest sample we could locate, a genetic study by Neumeister et al. (2006) reported fMRI of emotion perception in nine males with rMDD. Thus our sample of Males with rMDD ($n=16$) was more than double that of the majority of samples reported in the existing literature on fMRI of facial emotion perception.

4.4. Conclusions

Apart from our prior work (Briceño et al., 2015), it seems that very few other studies have examined the separate and interactive effects of Sex and MDD Diagnosis on brain activity during facial emotion perception. To our knowledge, this study was the first to explicitly examine Sex differences in neural processing of specific facial emotions in patients with rMDD and in interaction with HCs. Our results highlight the importance of the superior frontal gyrus in sex by diagnosis interactions for emotion perception, with a pattern of decreased activation in the Male rMDD group and increased activation in Females HCs relative to their sex-matched counterparts. Our results of significant interactions between Sex and Diagnosis for the Sadness and Neutral contrasts highlight the importance of examining sex differences in affective/salience circuitry. These results support, replicate, and extend those of a previous study with young adults in the active phase of MDD (Briceño et al., 2015), and therefore suggest that they may represent trait vulnerability or residual scar effects. Furthermore, we suggest that inconsistencies in previously reported findings in studies of MDD (Müller et al., 2017) may be explained, at least in part, by underlying interactions with Sex and smaller sample sizes. Our study provides further support for the

necessity of considering Sex effects in studies of MDD, regardless of disease state, as they may represent trait vulnerabilities. Future prospective and longitudinal research can determine whether they are indeed trait vulnerability effects or residual scar effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the individuals that participated in this study. We thank the Multifaceted Explorations of the Neurobiology of Depressive Disorders laboratory (MEND2, Kelly A Ryan, Laura B. Gabriel, Anne L. Weldon, Kortni K. Meyers, Erica Hymen, Bethany Pester, and Kristy A. Skerrett,) for assistance in data collection and diagnostic interviews.

Funding

This work was supported by funding provided by NIMH grant RO1 091811 (SAL).

References

- Arnone D, McKie S, Elliott R, Thomas EJ, Downey D, Juhasz G, Anderson IM. Increased amygdala responses to sad but not fearful faces in major depression: Relation to mood state and pharmacological treatment. *American Journal of Psychiatry*. 2012; 169(8):841–850. DOI: 10.1176/appi.ajp.2012.11121774 [PubMed: 22854930]
- Beck, AT. *Depression: Causes and treatment*. Philadelphia, PA: University of Pennsylvania Press; 1967.
- Briceño EM, Rapport LJ, Kassel MT, Bieliauskas LA, Zubieta JK, Weisenbach SL, Langenecker SA. Age and gender modulate the neural circuitry supporting facial emotion processing in adults with Major Depressive Disorder. *American Journal of Geriatric Psychiatry*. 2015; 23(3):304–313. DOI: 10.1016/j.jagp.2014.05.007 [PubMed: 25085721]
- Briceño EM, Weisenbach SL, Rapport LJ, Hazlett KE, Bieliauskas LA, Haase BD, Langenecker SA. Shifted inferior frontal laterality in women with major depressive disorder is related to emotion-processing deficits. *Psychological Medicine*. 2013; 43(7):1433–1445. DOI: 10.1017/s0033291712002176 [PubMed: 23298715]
- Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: From environment to theory of mind. *Neuron*. 2008; 58(3):306–324. DOI: 10.1016/j.neuron.2008.04.017 [PubMed: 18466742]
- du Boisgueheneuc F, Levy R, Volle E, Seassau M, Duffau H, Kinkingnehun S, Dubois B. Functions of the left superior frontal gyrus in humans: A lesion study. *Brain*. 2006; 129:3315–3328. DOI: 10.1093/brain/awl244 [PubMed: 16984899]
- Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America*. 2016; 113(28):7900–7905. DOI: 10.1073/pnas.1602413113 [PubMed: 27357684]
- Fales CL, Barch DM, Rundle MA, Mintun MA, Mathews J, Snyder AZ, Sheline YI. Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. *Journal of Affective Disorders*. 2009; 112(1–3):206–211. DOI: 10.1016/j.jad.2008.04.027 [PubMed: 18559283]
- Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(26):10046–10051. DOI: 10.1073/pnas.0604187103 [PubMed: 16788060]
- Fu CHY, Williams SCR, Cleare AJ, Brammer MJ, Walsh ND, Kim J, Bullmore ET. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: A prospective, event-

- related functional magnetic resonance imaging study. *Archives of General Psychiatry*. 2004; 61(9): 877–889. DOI: 10.1001/archpsyc.61.9.877 [PubMed: 15351766]
- Gotlib, IH., Hammen, CL. *Psychological aspects of depression: Toward a cognitive-interpersonal integration*. Oxford, England: Wiley; 1992.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160(4):636–645. DOI: 10.1176/appi.ajp.160.4.636 [PubMed: 12668349]
- Hale WW. Judgment of facial expressions and depression persistence. *Psychiatry Research*. 1998; 80(3):265–274. DOI: 10.1016/s0165-1781(98)00070-5 [PubMed: 9796942]
- Hankin B, Abramson LY. Development of gender differences in depression: An elaborated cognitive vulnerability-transactional stress theory. *Psychological Bulletin*. 2001; 127:773–796. doi:<http://dx.doi.org/10.1037/0033-2909.127.6.773>. [PubMed: 11726071]
- Jenkins LM, Kassel MT, Gabriel LB, Gowins JR, Hymen EA, Verges A, Langenecker SA. Amygdala and dorsomedial hyperactivity to emotional faces in youth with remitted Major Depression. *Social Cognitive and Affective Neuroscience*. 2016; 11(5):736–745. DOI: 10.1093/scan/nsv152 [PubMed: 26714574]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17(2):825–841. DOI: 10.1006/nimg.2002.1132 [PubMed: 12377157]
- Joormann J, Gotlib IH. Is this happiness I see? Biases in the identification of emotional facial expressions in depression and social phobia. *Journal of Abnormal Psychology*. 2007; 115:705–714. DOI: 10.1037/0021-843X.115.4.705
- Kalisch R. The functional neuroanatomy of reappraisal: Time matters. *Neuroscience and Biobehavioral Reviews*. 2009; 33(8):1215–1226. DOI: 10.1016/j.neubiorev.2009.06.003 [PubMed: 19539645]
- Kanske P, Heissler J, Schonfelder S, Bongers A, Wessa M. How to regulate emotion? Neural networks for reappraisal and distraction. *Cerebral Cortex*. 2011; 21(6):1379–1388. DOI: 10.1093/cercor/bhq216 [PubMed: 21041200]
- Kanske P, Heissler J, Schonfelder S, Wessa M. Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence. *Neuroimage*. 2012; 61(3):686–693. DOI: 10.1016/j.neuroimage.2012.03.089 [PubMed: 22613776]
- Kerestes R, Bhagwagar Z, Nathan PJ, Meda SA, Ladouceur CD, Maloney K, Blumberg HP. Prefrontal cortical response to emotional faces in individuals with major depressive disorder in remission. *Psychiatry Research: Neuroimaging*. 2012; 202:30–37. DOI: 10.1016/j.psychres.2011.11.004 [PubMed: 22595508]
- Kessler, RC. *Epidemiology of depression*. New York: Guildford Press; 2002.
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry*. 2005; 62:539–602. DOI: 10.1001/archpsyc.62.6.593
- Klumpp H, Angstadt M, Phan KL. Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biological Psychology*. 2012; 89(1):273–276. DOI: 10.1016/j.biopsycho.2011.10.010 [PubMed: 22027088]
- Kohler CG, Hoffman LJ, Eastman LB, Healey K, Moberg PJ. Facial emotion perception in depression and bipolar disorder: A quantitative review. *Psychiatry Research*. 2011; 188(3):303–309. DOI: 10.1016/j.psychres.2011.04.019 [PubMed: 21601927]
- Langenecker SA, Bieliasukas LA, Rapport LJ, Zubieta JK, Wilde EA, Berent S. Face emotion perception and executive functioning deficits in depression. *Journal of Clinical and Experimental Neuropsychology*. 2005; 27(3):320–333. DOI: 10.1080/13803390490490515720 [PubMed: 15969355]
- Langenecker SA, Caveney AF, Giordani B, Young EA, Nielson KA, Rapport LJ, Zubieta JK. The sensitivity and psychometric properties of a brief computer-based cognitive screening battery in a depression clinic. *Psychiatry Research*. 2007; 152(2–3):143–154. DOI: 10.1016/j.psychres.2006.03.019 [PubMed: 17445911]

- Langenecker SA, Saunders EFH, Kade AM, Ransom MT, McInnis MG. Intermediate: Cognitive phenotypes in bipolar disorder. *Journal of Affective Disorders*. 2010; 122:285–293. [PubMed: 19800130]
- LeMoult J, Joormann J, Sherdell L, Wright Y, Gotlib IH. Identification of emotional facial expressions following recovery from depression. *Journal of Abnormal Psychology*. 2009; 118:828–833. DOI: 10.1037/a0016944 [PubMed: 19899852]
- Leyman L, De Raedt R, Schacht R, Koster EHW. Attentional biases for angry faces in unipolar depression. *Psychological Medicine*. 2006; 37:339–402. doi:<http://dx.doi.org/10.1017/S003329170600910X>.
- Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology*. 2005; 1:167–195. DOI: 10.1146/annurev.clinpsy.1.102803.143916
- Maxwell, E. Clinical Neurogenetics Branch, Intramural Research Program. National Institute of Mental Health; 1992. Family Interview for Genetic Studies (FIGS): A Manual for FIGS.
- Mikhailova ES, Vladimirova TV, Iznak AF, Tsusulkovskaya EJ, Sushko NV. Abnormal recognition of facial expression of emotions in depressed patients with major depressive disorder and schizotypal personality disorder. *Biological Psychiatry*. 1996; 40:697–705. DOI: 10.1016/0006-3223(96)00032-7 [PubMed: 8894061]
- Miller CH, Hamilton JP, Sacchet MD, Gotlib IH. Meta-analysis of functional neuroimaging of Major Depressive Disorder in youth. *Jama Psychiatry*. 2015; 72(10):1045–1053. DOI: 10.1001/jamapsychiatry.2015.1376 [PubMed: 26332700]
- Montagne B, Kessels RPC, Frigerio E, de Haan EHF, Perrett DI. Sex differences in the perception of affective facial expressions: do men really lack emotional sensitivity? *Cognitive processing*. 2005; 6(2):136–141. DOI: 10.1007/s10339-005-0050-6 [PubMed: 18219511]
- Müller VI, Cieslik EC, Serbanescu I, Laird AR, Fox PT, Eickhoff SB. Altered brain activity in unipolar depression revisited: Meta-analyses of neuroimaging studies. *Jama Psychiatry*. 2017; 74(1):47–55. [PubMed: 27829086]
- Neumeister A, Drevets WC, Belfer I, Luckenbaugh DA, Henry S, Bonne O, Charney DS. Effects of alpha(2C)-adrenoreceptor gene polymorphism on neural responses to facial expressions in depression. *Neuropsychopharmacology*. 2006; 31(8):1750–1756. DOI: 10.1038/sj.npp.1301010 [PubMed: 16407897]
- Norbury R, Selvaraj S, Taylor MJ, Harmer C, Cowen PJ. Increased neural response to fear in patients recovered from depression: A 3T functional magnetic resonance imaging study. *Psychological Medicine*. 2010; 40(3):425–432. DOI: 10.1017/s0033291709990596 [PubMed: 19627640]
- Nurnberger JI, Blehar MC, Kaufmann CA, Yorkcooler C, Simpson SG, Harkavyfriedman J, Ritz AL. Diagnostic Interview for Genetic Studies: Rationale, unique features, and training. *Archives of General Psychiatry*. 1994; 51(11):849–859. [PubMed: 7944874]
- Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends in Cognitive Sciences*. 2005; 9(5): 242–249. DOI: 10.1016/j.tics.2005.03.010 [PubMed: 15866151]
- Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. *Biological Psychiatry*. 2005; 57(3):210–219. DOI: 10.1016/j.biopsych.2004.10.030 [PubMed: 15691521]
- Rapport LJ, Friedman SL, Tzelepis A, Van Voorhis A. Experienced emotion and affect recognition in adult attention-deficit hyperactivity disorder. *Neuropsychology*. 2002; 16(1):102–110. DOI: 10.1037//0894-4105.16.1.102 [PubMed: 11853351]
- Russell JA, Bachorowski JA, Fernandez-Dols JM. Facial and vocal expressions of emotion. *Annual Review of Psychology*. 2003; 54:329–349. DOI: 10.1146/annurev.psych.54.101601.145102
- Schienze A, Schafer A, Stark R, Walter B, Vaitl D. Gender differences in the processing of disgust- and fear-inducing pictures: An fMRI study. *NeuroReport*. 2005; 16:277–280. [PubMed: 15706235]
- Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *NeuroReport*. 2001; 16:277–280.
- Smith SM. Fast robust automated brain extraction. *Human Brain Mapping*. 2002; 17(3):143–155. DOI: 10.1002/hbm.10062 [PubMed: 12391568]

- Stevens JS, Hamann S. Sex differences in brain activation to emotional stimuli: A meta-analysis of neuroimaging studies. *Neuropsychologia*. 2012; 50:1578–1593. DOI: 10.1016/j.neuropsychologia.2012.03.011 [PubMed: 22450197]
- Surguladze SA, Young AW, Senior C, Brebion G, Travis MJ, Phillips ML. Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology*. 2004; 18(2):212–218. DOI: 10.1037/0894-4105.18.2.212 [PubMed: 15099143]
- Thomas EJ, Elliott R, McKie S, Arnone D, Downey D, Juhasz G, Anderson IM. Interaction between a history of depression and rumination on neural response to emotional faces. *Psychological Medicine*. 2011; 41(9):1845–1855. DOI: 10.1017/s0033291711000043 [PubMed: 21306660]
- Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, Nelson C. The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*. 2009; 168(3):242–249. DOI: 10.1016/j.psychres.2008.05.006 [PubMed: 19564050]
- Victor TA, Furey ML, Fromm SJ, Ohman A, Drevets WC. Relationship between amygdala responses to masked faces and mood state treatment in major depressive disorder. *Archives of General Psychiatry*. 2010; 67:1128–1138. DOI: 10.1001/archgenpsychiatry.2010.144 [PubMed: 21041614]
- Wade TJ, Cairney J, Pevalin DJ. Emergence of gender differences in depression during adolescence: National panel results from three countries. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002; 41:190–198. DOI: 10.1097/00004583-200202000-00013 [PubMed: 11837409]
- Weisenbach SL, Rapport LJ, Briceno EM, Haase BD, Vederman AC, Bieliauskas LA, Langenecker SA. Reduced emotion processing efficiency in healthy males relative to females. *Social Cognitive and Affective Neuroscience*. 2014; 9(3):316–325. DOI: 10.1093/scan/nss137 [PubMed: 23196633]
- Weisenbach SL, Rapport LJ, Briceno EM, Hasse BD, Vederman AC, Bieliauskas LA, Langenecker SA. Reduced emotion processing efficiency in healthy males relative to females. *Social Cognitive & Affective Neuroscience*. 2014; 9:316–325. DOI: 10.1093/scan/nssl37 [PubMed: 23196633]
- Whittle S, Yucel M, Yap MBH, Allen NB. Sex differences in the neural correlates of emotion: Evidence from neuroimaging. *Biological Psychology*. 2011; 87(3):319–333. DOI: 10.1016/j.biopsycho.2011.05.003 [PubMed: 21600956]
- Wright SL, Langenecker SA, Deldin PJ, Rapport LJ, Nielson KA, Kade AM, Zubieta JK. Gender-specific disruptions in emotion processing in younger adults with depression. *Depression and Anxiety*. 2009; 26(2):182–189. DOI: 10.1002/da.20502 [PubMed: 18800371]
- Xu J, Rees G, Yin X, Song C, Han Y, Ge H, Liu S. Spontaneous neuronal activity predicts intersubject variations in executive control of attention. *Neuroscience*. 2014; 263:181–192. DOI: 10.1016/j.neuroscience.2014.01.020 [PubMed: 24447598]
- Yao ZJ, Yan R, Wei MB, Tang H, Qin JL, Lu Q. Gender differences in brain activity and the relationship between brain activity and differences in prevalence rates between male and female major depressive disorder patients: A resting-state fMRI study. *Clinical Neurophysiology*. 2014; 125(11):2232–2239. DOI: 10.1016/j.clinph.2014.03.006 [PubMed: 24746685]

Highlights

- Females are twice as likely as males to have major depressive disorder (MDD)
- Potentially due to sex differences in facial emotion processing
- We used fMRI to study effects of sex and MDD history on facial emotion processing
- Interaction of sex and diagnosis seen in superior frontal and left temporal gyri
- Consideration of sex is important for examining neural mechanisms of emotion in MDD

Figure 1.
fMRI results of the interaction of Diagnosis and Sex

Figure 2.
fMRI results of the main effect of Sex for Anger, Fear, Happy, Neutral and Sad contrasts in the rMDD group only.

Note. White regions show significant activity for all five contrasts.

Figure 3.
Results displayed through bilateral amygdala ROI at $p < .05$, $k = 15$.

Figure 4.

Bar graph of left and right amygdala ROI activity for Sad contrast by Diagnosis and Sex. Covariates included in the data are Sad accuracy and Site.

Table 1

Mean Demographic Characteristics for each Diagnosis and Sex

	HC		rMDD	
	Male	Female	Male	Female
N	15	25	16	32
Age (SD) *	20.67 (1.76)	21.00 (1.63)	20.69 (1.62)	21.72 (1.28)
Education (SD)	14.20 (1.32)	15.00 (1.35)	14.50 (1.71)	14.71 (1.13)
VIQ (SD)	103.20 (10.02)	107.73 (8.43)	107.81 (9.49)	105.07 (10.77)
Caucasian	9	21	10	23
Asian	4	3	3	3
African American	0	1	1	3
Hispanic/Latino	2	0	1	1
Multiple races	0	0	0	2
HDRS (SD) *	0.40 (1.12)	0.40 (0.71)	1.47 (1.85)	2.03 (2.28)
Age 1 st episode	-	-	16.87 (3.25)	16.10 (3.62)
Ever therapy Y/N	-	-	12/19	31/25
Ever medicated Y/N	-	-	6/25	10/47

Note. HC = healthy control, rMDD = remitted Major Depressive Disorder, VIQ = verbal intelligence quotient, HDRS = Hamilton Depression Rating Scale.

* rMDD had higher HDRS scores than HC, $F(1, 83) = 12.39$, $p = .001$, $\eta^2 = .13$; Females were on average 8.64 months older than males, $F(1, 84) = 3.96$, $p = .05$, $\eta^2 = .05$.

Table 2

fMRI Results of the Interaction between Diagnosis and Sex

Contrast	Lobe/gyrus	BA	MNI coordinates			Peak Z	Cluster	Follow-up analysis
			x	y	z	Z	K	
Sad	frontal							
	superior		-					M HC>F HC ^{**} ; M
		6	10	10	64	3.65	59	rMDD<F rMDD [*]
	temporal							
	middle		-		-			M HC<F HC [*] ; M
		21	50	2	16	2.28	89	rMDD>F rMDD [*]
Neutral	subcortical							
	midbrain,		-		-			M HC<F HC ^{***} ; M
	PHG		12	34	10	4.70	163	rMDD>F rMDD [*]
	midbrain,		-		-			M HC<F HC ^{**} ; M
	PHG		12	26	16	4.33	241	rMDD>F rMDD ^{**}
Sad	frontal							
	superior		-					
		6	-2	12	68	4.05	221	
	subcortical							
	dorsomedial		-					M HC>F HC [*] ; M
	thal		16	16	18	3.54	95	rMDD<F rMDD [*]

Note.

* $p < .05$,

** $p < .01$,

*** $p < .001$

PHG= parahippocampal gyrus, thal= thalamus. Conversion of cluster number to size is by $k \times 2 \times 2 \times 2$, or k^4 for mm^3 .