An fMRI Study of Emotional Face Processing in Adolescent Major Depression

A Thesis

SUBMITTED TO THE FACULTY OF

UNIVERSITY OF MINNESOTA

BY

Leah M. Jappe

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF ARTS

Advisers: Bonnie Klimes-Dougan, PhD, Scott Crow, MD

February 2013

Acknowledgments

I would like to acknowledge several people who helped make this project possible. A special thank you to Drs. Bonnie Klimes-Dougan and Katie Cullen for allowing me to explore their adolescent neuroimaging data set and for providing support throughout this endeavor. I would also like to thank Ruskin Hunt for his invaluable guidance in the area of neuroimaging statistical analysis and Emily Noack for her assistance preparing the literature review. Finally, thank you to Drs. Scott Crow, Bonnie Klimes-Dougan, and Monica Luciana for taking the time to serve as members of my final exam committee.

Abstract

OBJECTIVE: Major Depressive Disorder (MDD) is a serious, often chronic illness associated with significant impairment and suicide. MDD often begins during adolescence when brain areas that regulate emotion processing are still maturing. To expand upon our limited understanding of the neurobiological underpinnings of MDD early on in development, this study examined function within fronto-limbic neural circuits in response to an emotional faces task among depressed adolescents and healthy controls (HC) using functional magnetic resonance imaging (fMRI). **METHOD**: 34 adolescents with MDD (12 medicated, 22 unmedicated) and 16 healthy age and gender matched controls completed an emotional faces task where BOLD response was examined when viewing happy and fearful faces (presented in a block design) during fMRI. Scanning was completed using a 3.0 Tesla scanner. Data preprocessing and analysis was carried out using FEAT in FSL. Whole brain group level analyses were conducted using a mixed-effects model (FLAME) with cluster-wise significant testing (min $Z=2.32$; cluster significance = $p<0.05$, corrected). **RESULTS**: In response to viewing fearful versus happy faces, MDD showed reduced activation in areas of the right thalamus, right insula, and right hippocampus compared to HC. **CONCLUSION**: Results suggest that emotion processing in adolescent MDD is associated with abnormalities in subcortical and paralimbic brain regions within the broader fronto-limbic neural network. It is possible that these findings reflect deficits in depressed adolescents' ability to elicit cognitive control from higher cortical regions and to accurately respond to and process the emotional significance of fearful stimuli.

Table of Contents

List of Tables

List of Figures

Major depressive disorder (MDD) is a serious mental illness characterized by a heterogeneous presentation of symptoms that include depressed mood and anhedonia in addition to fatigue; sleep, appetite, and motor disturbances; cognitive alterations; feelings of worthlessness; and thoughts of suicide (American Psychiatric Association, 2000). MDD is a common psychiatric disorder with lifetime prevalence rates estimated between approximately 15% and 20% (Birmaher, Arbelaez, & Brent, 2002; Greenberg et al., 2003; Kessler et al., 2003; Kessler et al., 2010; Nes et al., 2013). On average, disease onset occurs during early adulthood (Kessler et al., 2010). However, MDD often develops during adolescence (Birmaher et al., 2002; Kessler, Avenevoli, & Ries Merikangas, 2001) where it frequently follows a chronic course and places youth at risk for significant morbidity and mortality across the lifespan (Berndt et al., 2000; Zisook et al., 2007). According to the National Comorbidity Survey, Adolescent Supplement (NCS-A), 11% of adolescents will experience a depressive episode before 18 years of age and 3.3% of adolescents will experience an episode classified as severe (Merikangas et al., 2011). Of those who develop MDD, most will experience recurrent episodes (Hirschfeld, 2012; Keller et al., 1992). According to Kessler, Birnbaum, Bromet, Hwang, Sampson and Shahly (2010), individuals with MDD report an average of 18.6 major depressive episodes during their lifetimes that typically last approximately 4-7 months (Kessler et al., 2003; Kessler et al., 2010).

The World Health Organization listed MDD as a leading cause of disability among adolescents and adults (World Health Organization, 2008). MDD has been linked to major role impairments (Kessler et al., 2003), significant use of health care resources (Kessler et al., 2010), high treatment costs (Kessler, 2012), reduced life satisfaction (Nes

et al., 2013) and high rates of mortality, including death by suicide (Simon & Hales, 2006). Thus, negative outcomes associated with MDD affect all aspects of life: personal, social, occupational, and may result in chronic suffering and early death.

Vulnerability for MDD has been attributed to both environmental (e.g., stressful life events) and genetic factors (Lewinsohn, Allen, Seeley, & Gotlib, 1999; Lopez-Leon et al., 2008; Monroe, Rohde, Seeley, & Lewinsohn, 1999; Widom, DuMont, & Czaja, 2007). Regardless of its origins, significant evidence from neuroscience research indicates that aspects of depressive symptomology are mediated by abnormalities in underlying neurobiological structure and function (Mayberg, 1997; Tanti & Belzung, 2010a). Of particular importance to this study, abnormal processing of emotional stimuli, which is regulated by fronto-limbic brain circuits, has been consistently implicated in the context of major depression and is thought to increase risk of disease development, maintenance and relapse (Foland-Ross & Gotlib, 2012a; Mathews & MacLeod, 2005).

Given the individual and societal burdens that result from this psychiatric illness, research that further advances our understanding of the etiological and maintaining factors contributing to MDD is critically important. In particular, examining neurobiological underpinnings of emotion processing abnormalities in adolescent MDD is necessary for several reasons. First, the prognosis for depression is particularly poor when the problems are evident early on during development (Brent et al., 1998; Gollan, Raffety, Gortner, & Dobson, 2005; Zisook et al., 2007). For example, early onset depression is associated with increased symptom severity, greater likelihood of relapse, and increased suicidality (Hollon et al., 2006). In addition, neural pruning occurs throughout adolescence and growing evidence suggests that fronto-limbic brain circuits

controlling emotion processing continue to undergo significant maturation and refinement during this time (Lenroot & Giedd, 2006; Romeo & McEwen, 2006). Examining biological mechanisms of emotion regulation early in the disease course, uncompromised by the scarring effects of chronic illness, may help us identify neurobiological markers unique to adolescent MDD. Doing so has the potential to improve our understanding of treatment targets and thus lead to the development of innovative early intervention strategies that take advantage of still-malleable neural systems prior to maturity.

This paper provides background regarding what is known about emotional processing deficits and the neural circuits underlying them in MDD. It then presents a study investigating brain function in response to an emotional processing task in depressed adolescents.

Emotion Processing Deficits in MDD: Evidence from Behavioral Research

There is significant evidence from non-neurobiological research that suggests individuals with MDD possess biases towards processing negative over more positively valenced emotional stimuli. Specifically, those with MDD exhibit alterations in attention towards negative cues in addition to abnormalities in memory and interpretation of emotional information. The studies presented below briefly illustrate some the cognitive biases, present at both basic (Suslow et al., 2010) and higher levels of cognitive processing (Mathews & MacLeod, 2005), that have been indentified using behavioral measures.

Tasks that examine unconscious processing of emotional cues (e.g., dot-probe task, Emotional Stroop task, lexical decision task) have tended to suggest that major

depression is not associated with *automatic* biases in attention towards negative emotions (B. P. Bradley, Mogg, Millar, & White, 1995; Lim & Kim, 2005; Mathews, Ridgeway, & Williamson, 1996; Mogg, Bradley, & Williams, 1995) although recent neuroimaging studies suggest otherwise (Victor, Furey, Fromm, Ohman, & Drevets, 2010). Regardless, individuals with depression do appear to possess altered attention towards negative information presented at the conscious level, so termed mood-congruent attention bias. For example, Gotlib et al. (2004) examined processing of positive and negative facial stimuli in clinically diagnosed depression and social phobia using a facial expression dot-probe task. During this task, participants were shown pictures of emotional faces (sad, happy, angry, neutral) side by side on a computer screen and subsequently asked to identify the location of a dot presented in the same location as one of the previously viewed images. Quicker response times to dots presented in the same location as negative emotional faces reflected biased attention towards negative stimuli. Using this method, Gotlib et al. (2004) found that, compared to anxious and healthy controls, depressed participants were significantly faster at locating the probes presented in the same location as sad faces than they were for the happy or angry faces. This same pattern of results has been replicated in other studies employing verbal stimuli as well (Bradley, Mogg, & Lee, 1997; Fritzsche et al., 2010).

In addition to findings observed during acute phases of the illness, attention biases towards sad stimuli have been found in individuals who have recovered from the illness (Fritzsche et al., 2010; Joormann, Siemer, & Gotlib, 2007) and in individuals who possess a family history of depression (Joormann, Talbot, & Gotlib, 2007; Kujawa et al., 2011), indicating that biases towards negative stimuli may place individuals at increased

risk for MDD development (Koster et al., 2006). Similarly, depressed individuals have been found to spend more time selectively attending to stimuli with negative themes than controls when studied using eye-track paradigms (Caseras, Garner, Bradley, & Mogg, 2007; Eizenman et al., 2003), implying that sustained attention biases may also function to maintain depressive symptoms (Bradley et al., 1997).

Individuals with MDD appear to possess biases in both implicit and explicit memory for emotionally-laden information (Bradley et al., 1995; Gilboa-Schechtman, Erhard-Weiss, & Jeczemien, 2002; Watkins, Martin, & Stern, 2000). For example, using self-referential encoding and recall tasks, recovered and acutely ill individuals with MDD have been shown to recall a higher proportion of sad words and a lower proportion of positive words than anxious or healthy controls (Fritzsche et al., 2010; Gotlib et al., 2004). By measuring self-perceptions and response latencies in addition to recall, this method ensures that memory biases are not confounded by differences in individual endorsement or overall memory performance.

Lastly, consistent with cognitive theories of MDD, depressed individuals tend to both prospectively (Lawson, MacLeod, & Hammond, 2002) and retrospectively (Mathews & MacLeod, 2005) interpret events as being more negative than controls. This is illustrated by Lawson et al. (2002) who found that higher depression severity scores were associated with greater eye-blink magnitudes in response to ambiguous cues. The magnitude of the eye-blink reflex is a well-validated measure of emotional valence, where more negative stimuli evoke larger eye-blink responses (Bradley, Cuthbert, & Lang, 1991; Lang, Bradley, & Cuthbert, 1990).

Taken together, findings from the studies highlighted above indicate that MDD is associated with biases in regards to attention, memory, and interpretation of negative stimuli, which likely influence emotional pathology in a causal manner (Mathews & MacLeod, 2005). It has been suggested that these biases result from alterations in both bottom-up emotional and top-down control neural processes (Foland-Ross & Gotlib, 2012b), functions which are regulated by fronto-limbic brain circuits.

Fronto-Limbic Neural Circuitry

The fronto-limbic neural network, as proposed by Mayberg (1997, 2003) in her dysregulation model of depression, is composed of neocortical, subcortical and paralimbic brain structures that interact to regulate emotional reactivity and affective behavior. Specifically, neocortial structures include the dorsal-lateral prefrontal cortex, inferior parietal cortex, and dorsal and posterior cingulate cortex. These higher order cortical regions play a regulatory role in emotion processing and are thought to be associated with the cognitive and attentional abnormalities observed in MDD (Halari et al., 2009).

Paralimbic structures include the medial orbital frontal cortex, subgenual cingulate cortex, hypothalamus, hippocampus, insular cortex, and amygdala. These more primitive limbic structures form the foundation of our emotional system, where they are responsible for responding to emotional cues. In particular, the amygdala rapidly reacts to and evaluates the emotional saliency of stimuli (Victor et al., 2010) and is involved in processing facial displays of affect (Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006). For example, neuroimaging studies have consistently shown that the amygdala is active in response to happy, fearful, and sad faces in healthy adults (Fusar-Poli et al.,

2009). A core function of the subgenual cingulate cortex is to regulate amygdala activity, in effect reducing high emotional responsivity to threatening stimuli (Phillips, Drevets, Rauch, & Lane, 2003). The insula has been associated with processing the subjective experience of emotions, particularly feelings of anger and disgust (Suzuki, 2012), and it is also thought to play a role in understanding emotions of others (Wicker et al., 2003). Other limbic structures (i.e., hypothalamus, orbital frontal cortex, hippocampus) regulate autonomic and endocrine function (e.g., hypothalamic-pituitary-adrenal axis activity), emotional decision-making, and function in emotional memory formation (Bechara, Damasio, & Damasio, 2000; Bechara, 2004; Price & Drevets, 2010).

Individual structures *within* neocortical and paralimbic regions are themselves reciprocally interconnected; however, via direct anatomical connections, the subcortical structures (i.e., rostral cingulate cortex, striatum, and thalamus) facilitate communication *between* areas of the cortex and limic system (Mayberg, 1997; Mayberg, 2003). The integrity of these individual fronto-limbic structures and the links between them collectively control emotional processing; therefore, dysfunction within or between components of this system can lead to affective disturbance.

In general, Mayberg suggests that depressive symptomatology is a consequence of hypo and hyperactivity in neorcortical and paralimbic structures respectfully (Mayberg, 1997; Stuhrmann, Suslow, & Dannlowski, 2011). Numerous neuroimaging studies have expanded upon the behavioral research of emotion processing in MDD and have provided significant support for this claim (e.g., Cullen et al., 2009; Cullen et al., 2010; Drevets, Price, & Furey, 2008; Greicius, 2008; Price & Drevets, 2012; Savitz & Drevets, 2009; Steingard et al., 2002).

Because, emotional facial expressions are 1) efficient at eliciting responses in fronto-limbic areas (Fusar-Poli et al., 2009), 2) may be particularly sensitive to processing biases in MDD (Stuhrmann et al., 2011), and 3) are of primary relevance to this present study, research in this area that has investigated alterations in brain regions specific to Mayberg's model is reviewed in detail. A majority of the studies presented employ the use of two different types of stimuli: masked and unmasked faces that examine neural activity to unconscious and conscious stimuli respectfully. This, in addition to differences in sample characteristics and statistical approaches, likely explain some of the heterogeneity of findings.

Alterations in Emotional Face Processing: Adult MDD

Most adult neuroimaging studies of emotion processing in response to faces have focused on the amygdala. Specifically, researchers have suggested that increased activity in the amygdala when viewing negative emotional faces may be a biomarker for MDD (Arnone et al., 2012; Victor et al., 2010).

For example, Arnone et al. (2012) compared blood-oxygen-level-dependent (BOLD) response in the amygdala in a large sample of moderately depressed adults to that of adults in remission and healthy controls. They found increased bilateral amygdala activity in those with acute depression symptoms when viewing sad vs. neutral faces. These authors further noted that depressed adults successfully treated with the antidepressant citrolapram showed normalization of this heightened amygdala activity, suggesting that the amygdala plays a specific role in processing sad faces in acute phases of depressive illness and is a region related to symptom improvement.

Whereas Arnone et al. (2012) investigated explicit processing of sad versus neutral emotions, Victor et al. (2010) examined unconscious emotion processing in depressed adults to that of healthy controls using a masked face paradigm. Results from this study suggested that individuals ill with depression and those who remitted from the illness had greater bilateral amygdala activity in response to sad faces outside of conscious awareness whereas healthy adults had greater left amygdala activity when unconsciously processing happy faces. Unlike Arnone et al. (2012) no group differences were found when comparing response to emotional faces presented explicitly.

Hyper amygdala responsivity to masked sad faces and hypo amygdala response to masked happy faces has been replicated by Suslow et al. (2010). In addition, increased left amygdala response to masked fearful faces has also been reported in adult MDD (Sheline et al., 200; Peluso et al., 2009). These results suggest that that biases for processing mood congruent emotional stimuli in depressed adults are present at the neural level outside of conscious awareness.

Aside from amygdala findings, other regions within the fronto-limbic neural circuit have been implicated in emotional face processing in MDD. For example, increased insula activity has been associated with viewing sad (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Suslow et al., 2010), fearful, angry (Zhong et al., 2011) and disgusted faces (S. A. Surguladze et al., 2010). Similarly, decreased functional activity has been observed in areas of the dorsal lateral PFC and orbital frontal cortex (Keedwell et al., 2005; Lawrence et al., 2004; Zhong et al., 2011). Findings within the cingulate have been mixed (Stuhrmann et al., 2011).

The studies illustrated above present data that were based on adult patients with

MDD. It is possible that findings in this specific population may not be relevant to MDD at different times during development. For this reason, researchers have begun to investigate emotion processing in depressed adolescents using similar neuroimaging methods.

Alterations in Emotional Face Processing: Adolescent MDD

Compared to the adult literature, there have only been a handful of investigations examining neural correlates of emotional face processing in adolescents, and it is thus an area that remains severely understudied. Monk et al. (2008) found that children and adolescents at high risk for developing MDD had greater activation in the amygdala and nucleus accumbens when passively viewing fearful faces. Constraining attention to the same images resulted in increased medial PFC activation and concurrent normalization of the amygdala response, suggesting that directed attention towards emotional stimuli may engage higher order cognitive regions and improve emotion regulatory processing in those at risk for MDD.

In a sample of medication naïve, depressed adolescents without comorbid psychiatric diagnoses, Yang et al. (2010) employed an emotional faces matching task and found that adolescent MDD was associated with increased anterior cingulate cortex and left amygdala activation in response to fearful, sad, and happy faces as compared to healthy controls. In this task, participants are presented with a picture of a human face and then asked to match the emotion on that particular face to one of two additional faces.

Beesdo et al. (2009) compared amygdala activity in depressed and anxious youth using an emotional faces task that required varying levels of attentive control. When

passively viewing emotional faces, Beesdo et al. (2009) found that adolescents with MDD had decreased (and opposite) bilateral amygdala response compared to both healthy and anxious comparison groups. However, when selectively attending to the emotional valence of each image (ensured by having participants rate the severity of the emotion displayed on a likert scale, e.g., "How fearful is this face?"), MDD and anxious participants showed similarly increased left amygdala activity. Results suggest that, while passively viewing faces differentiates psychiatric disorders, attending to the emotional salience of the stimuli results in limbic hyperactivation common to both depression and anxious symptoms in adolescents.

Examining changes in brain function in adolescent MDD following antidepressant treatment, Tao et al (2012) concluded that increased brain activation to fearful faces in amygdalar, orbitofrontal, and subgenual cingulate regions normalized following administration of an 8-week fluoxetine trial.

Taken together, the relatively few studies investigating emotional face processing in adolescent MDD implicate alterations in areas of the fronto-limbic network, most notably the amygdala; however, more research is needed to clarify inconsistencies in regards to directionality of the abnormal responses observed.

Effects of Co-morbid Anxiety and Antidepressants

As illustrated by the study by Tao et al. (2012), the use of antidepressant medications alter brain activity in areas important for emotional regulation (Tanti & Belzung, 2010b), specifically where amygdala reactivity to fearful and happy faces has been shown to diminish with antidepressant use (Sheline et al., 2001; Tao et al., 2012). In addition, alterations in fronto-limbic neural circuitry is not unique to MDD. For example,

increased amygdala response to emotional stimuli is well documented in anxiety disorders (e.g., (Wolfensberger, Veltman, Hoogendijk, Boomsma, & de Geus, 2008). It is therefore critically important that studies investigating emotion processing and associated neural function in MDD account for the potential confounding effects of antidepressant use and psychiatric comorbidity.

In depressed adolescents, only three known studies to date have controlled for concurrent anxiety and medication status when examining fronto-limbic circuitry with emotional faces tasks (Beesdo et al., 2009; Tao et al, 2012, Yang et al, 2010). While findings from these studies suggest that heightened amygdala reactivity is present in medication-free, diagnostically pure MDD, additional research is needed to confirm these findings in adolescents and to explore other important regions within the fronto-limibic network in this population.

Overall, findings in adolescents appear consistent with the adult literature, suggesting that neural underpinnngs of MDD are consistent across development; however, the relatively sparse data investigating emotion processing in younger populations that account for confounding effects of psychotropic medication and co-morbid anxiety makes it difficult to draw any firm conclusions. As several authors note, additional research is critically needed (Tao et al., 2012; Yang et al., 2010). For this reason, the present study aimed to examine brain function in adolescents diagnosed with MDD in response to an emotional faces task using fMRI methodology.

Based on previous work in both adolescents and adults, it was hypothesized that, compared to healthy controls, participants with MDD would show increased amygdala activity and decreased prefrontal activity when viewing fearful versus happy facial

expressions, but that these findings would only be present when comparing controls to an unmedicated MDD subsample. It was also hypothesized that amygdala responsivity would be greatest among depressed individuals with a concurrent anxiety disorder. Lastly, it was expected that secondary structures within neocortical, subcortical, and paralimbic brain regions would be implicated.

Method

Participants

50 adolescents (34 with MDD and 16 HC), ages 12-20 years old (*M* = 15.8, *SD* =1.9), were recruited to participate in this study. Participants were predominately female (78%) and Caucasian (72%). A majority of participants (92%) were right handed. Study inclusion and exclusion was determined by an extensive screening process that included an initial phone screen, parent and child in-person diagnostic interviews, and a battery of self-report questionnaires (see Measures). All controls had to be free from any current or lifetime psychiatric disorder and could not have a family history of depression. Depressed adolescents were included if they met current DSM-IV-TR criteria for a primary diagnosis of major depressive disorder. Use of psychotropic medication was permitted and used by 35% of the depressed sample at the time of the study. 60% of MDD adolescents presented with a current co-morbid psychiatric disorder (21% endorsed symptoms consistent with more than one co-morbid diagnosis). Of those with psychiatric co-morbidity, Generalized Anxiety Disorder (29%) and Attention Deficit-Hyperactivity Disorder (15%) were endorsed most frequently. Individuals with a history of bipolar disorder, schizophrenia, of pervasive developmental disorder were excluded from study participation. Additional exclusion criteria consisted of full scale IQ less than 80 as

measured by the Wechsler Abbreviated Intelligence Scale (WASI; Wechsler, 1999), history of serious head injury, medical illness, medical instability, and any MRI contraindication.

Measures

Psychiatric and Intellectual Assessments

***Schedule for Affective Disorders and Schizophrenia for School-Age Children, present and lifetime version, K-SADS*-PL** (Kaufman et al., 1997). This study employed the K-SADS-PL, a semi-structured clinical interview used to assess current and lifetime DSM-IV-TR Axis 1 disorders in children and adolescents. The K-SADS-PL has been shown to have acceptable concurrent validity in addition to both interrater (93=100%) and test-retest (kappa = .63-1.0) reliability (Kaufman et al., 1997). All interviews were conducted by trained, graduate level (or higher) assessors. Training in how to administer the KSADS included KSDAS observation, participating in mock role-play interviews, and conducting interviews supervised by licensed providers. In order to maintain adherence to the instrument and to prevent assessor drift, weekly group supervision meetings were held in which individual cases were presented and discussed.

Beck Depression Inventory, second edition, BDI-II (Beck, Steer, & Brown, 1996). The BDI-II is a 21-item self-report questionnaire that measures severity of depressive symptoms. Each item is rated on a 0-3 scale with a maximum total score of 63. Total scores between 0-13 indicate minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression (Beck, Steer, Ball, & Ranieri, 1996). The BDI-II is a widely used instrument in psychiatric research and has been shown to

have adequate concurrent validity and high (a = .91) internal consistency (Beck et al., 1996).

Behavioral Paradigm (Emotional Faces Task)

All participants completed two 5.2 minute runs of an emotional faces task where standardized grayscale images of adult men and women with either fearful or happy expressions were presented in a block design format and contrasted with fixation blocks (Ekman & Friesen, 1976). Images were presented on a screen placed at the back of the scanner and then projected to participants by two mirrors attached to a standard head coil. Each run was identical in terms of order of item presentation and consisted of 13 24-second blocks (5 fixation (C), 4 happy (H), 4 fearful (F) presented in a counterbalanced fashion: CFHCHFCHFCFHC). During experimental blocks, fearful or happy images were presented for 200 msec and followed by 1300 msecs of either a fixation cross or an "o". During control blocks, fixation crosses were presented sequentially for 1500 msec. While facial expressions presenting numerous negative emotions have been shown to activate the amygdala (Fitzgerald et al., 2006), a key area of interest in this study, fearful stimuli were chosen based on research suggesting that amygdala response is more sensitive to viewing fearful faces than sad faces (Fusar-Poli et al., 2009; Sheline et al., 2001).

Image acquisition

Scanning was conducted using a research-dedicated 3.0 Tesla Siemens Trio scanner and 12-channel radio-frequency (RF) head coil. A high-resolution T1-weighted anatomical image was acquired for each participant using a magnetization prepared gradient echo sequence (MPRAGE; 224 coronal slices; TR = 2530ms; TE = 3.65ms; TI =

1100ms; flip angle = 7°; FOV=256mm, voxel size = 1x1x1mm; matrix size=256x256). Functional data were acquired using an echo planar imaging sequence (EPI) where 156 T2*-weighted whole brain functional volumes (34 3.9mm interleaved contiguous axial slices, AC-PC aligned with a -30° tilt, TR = 2000ms; TE = 28 ms; flip angle = 80°, FOV = 200mm; voxel size = 3.1 x 3.1 x 3.9 mm; matrix = 64x64) were obtained in conjunction with the emotional faces task.

Procedure

Depressed adolescents were recruited from inpatient and outpatient clinics at the University of Minnesota and from community advertisements. Healthy controls were recruited from flyers posted throughout the Minneapolis and St. Paul metro area. This study was approved by the University of Minnesota Institutional Review Board.

Interested participants underwent an initial phone screening to assess for basic inclusion and exclusion criteria. Those who appeared eligible were scheduled for a screening visit where they received additional study information, signed informed assent/consent and completed diagnostic and self-report assessments. Trained, graduate level assessors conducted separate K-SADS-PL interviews with the adolescent and one parent where diagnoses were based on a consensus between the two reports. Enrolled participants then completed a subsequent visit consisting of the MRI scan at the University of Minnesota Center for Magnetic Resonance Research, where both anatomical and functional images were collected.

During the emotional faces task, participants held a response pad in their right hand and were instructed to press a key with their pointer finger any time an ‘o’ appeared on the screen. This was done to ensure that participants were viewing all the stimuli and

that they remained attentive throughout the task. Following the MRI scan, participants received compensation for completing study procedures.

Statistical Analysis

Demographics and Clinical Data

Demographic and clinical variables were analyzed using a series of one-way Analyses of Variance (ANOVAs) and Chi-squared tests in SPSS (Version 19.0). Fisher's Exact Test was used to account for low frequency categorical data.

Functional Data

Imaging data were processed and analyzed using the FEAT package in FSL 4.1.9 (www.fmrib.ox.ac.uk). Functional data were visually inspected for movement-related artifacts, where volumes with relative displacement in excess of 1.5 mm in any direction were removed. Single volumes preceding and following excess displacement were also excluded. In total, 155 total volumes (1.9%) were not included in the analysis on account of movement. Images were preprocessed with high-pass temporal filtration (Gaussian-weighted least squares straight line fitting, sigma = 75s), motion (MCFLIRT) and slice timing correction (to adjust for timing differences in slice acquisition within each volume). EPI images were co-registered with each individual's anatomical image (brain extracted using BET and visually inspected for quality), normalized to Montreal Neurological Institute (MNI) standard space with FNIRT, and spatially smoothed (FWHM 6mm). A first level GLM analysis was employed to regress the model specified by the task onto the blood oxygen level dependent (BOLD) response of each participant. The two independent runs of the emotional faces tasks were combined at a second level of analysis using a fixed effects model that allows for within-subject, multi-session

analyses. Whole brain group level analyses were conducted using a mixed-effects model (FLAME). Cluster-wise significant testing was used where multiple comparison corrections were carried out using Gaussian random field theory (min Z=2.32; cluster significance = $p<0.05$, corrected). Group level analyses produced Z-score maps for comparisons between stimuli conditions.

Follow-up correlational analyses were run to examine associations between clinical variables and BOLD response. Percent signal change for significant clusters were extracted for each participant using Featquery. Pearson correlation coefficients were subsequently calculated using SPSS.

Results

Demographic and Clinical Characteristics

There were no differences in age [$F(2,47)=0.82$, $p=0.45$], gender [$\chi^2(2, N=50)=1.76$, $p=0.42$], race [$\chi^2(8, N=50)=5.88$, $p=1.00$], or handedness [$\chi^2(2, N=50)=1.52$, $p=0.36$] between HC and depressed participants. As expected, one-way ANOVA results indicated that groups differed significantly in regards to depression severity [$F(2,29)=9.73$, $p<0.01$]. Specifically, medicated ($M=23.50$, $SD=13.07$, $p<0.05$) and unmedicated depressed adolescents ($M=28.05$, $SD=14.19$, $p<0.01$) reported average BDI scores reflective of moderate depression (Beck et al., 1996), which were significantly higher than those observed in healthy controls ($M=3.71$, $SD=3.04$). There were also significant group differences in IQ [$F(2, 47)=7.15$, $p<0.01$], where unmedicated MDD participants ($M=98.95$, $SD=16.43$) had lower IQ scores than both medicated MDD ($M=114.17$, $SD=11.62$, $p<0.05$) and HC ($M=113.81$, $SD=11.44$, $p<0.01$). There were no differences in IQ between HC and medicated MDD ($p=0.98$). It is important to note that

IQ scores in unmedicated MDD participants were still within the average range of intellectual ability (Wechsler, 1999). The proportion of comorbidity between the two depressed groups did not differ significantly [$\chi^2(8, N=50)=0.40, p=0.84$]. Demographic and clinical information is presented in Table 1.

Imaging Results

Whole brain analyses examined four comparisons between task stimuli (fear > fixation, happy > fixation, happy > fear, fear > happy) separately for both the HC and full MDD groups to ensure that the task activated the expected regions. Analyses to examine differences in activation between the two groups were then conducted.

HC and Full MDD: Individual Analyses

BOLD response to fearful expressions in comparison to viewing fixation yielded significant clusters in both HC and MDD groups covering regions of the bilateral supramarginal gyrus and bilateral temporal occipital fusiform cortex. In addition, HC had increased activation in areas of the right middle temporal gyrus, left thalamus, left pariteal operculum, and left lateral occipital cortex. MDDs had additional clusters of activation to this contrast in areas of the posterior cingulate gyrus, paracingulate gyrus, right hippocampus, right parahippocampal gyrus, and right frontal pole.

BOLD response in the happy greater than fixation condition yielded significant clusters covering bilateral temporal occipital fusiform and parietal operculum cortices in HC. In the MDD sample, additional regions of activation included the right supramarginal gyrus, right frontal pole, anterior cingulate cortex and paracingulate gyrus. These two contrasts (fear > fixation, happy > fixation) compare brain activity to complex facial stimuli to that of simple, neutral, non-face stimuli; therefore, activation in these

areas, particularly the fusiform cortex, supramarginal gyrus, and middle temporal gyrus would be expected given their role in face perception, recognition and processing (Haxby, Hoffman, & Gobbini, 2000; Kanwisher & Yovel, 2006; Platek et al., 2006).

In HC, no significant clusters survived thresholding at the z=2.32, p<0.05 level of significance when examining activation to the fear greater than happy contrast. However, activation in areas of the right hemisphere including the temporal fusiform cortex and regions of the limbic system (parahippocampal gyrus, pallidum, putamen, thalamus, and amygdala) were present at a lower level of significance (z=1.96, p<0.05). In the full MDD sample, fear greater than happy contrasts yielded significant clusters in regions of the left temporal fusiform cortex, left middle temporal gyrus, left insular cortex, left amygdala, left hippocampus, left nucleus accumbens, left dorsal medial prefrontal cortex, bilateral superior parietal cortex, bilateral medial orbital frontal cortex and anterior cingulate cortex.

No significant clusters were observed for the happy greater than fear contrast for either group. Anatomical locations of peak activation for each significant cluster observed among all four conditions in HC and MDD individually are presented in Table 2.

HC and Full MDD: Group Analyses

No group differences in activation were found between HC and the full MDD group for any of the four contrasts. As previously mentioned, antidepressant medications alter fronto-limbic function (Tanti & Belzung, 2010b), specifically within the amygdala (Sheline et al., 2001; Tao et al., 2012). To explore whether medication use could account for the lack of differences observed within the full sample, subsequent analysis examined

the four contrasts between HC and both the medicated and unmedicated MDD groups separately.

HC and Medicated MDD: Group Analyses

There were no group differences between the HC and Medicated MDD groups for any of the four contrasts.

HC and Unmedicated MDD: Group Analyses

Group differences were not observed between the HC and unmedicated MDD groups on either emotion versus fixation contrast.

Group comparison for the fear greater than happy contrast indicated that unmedicated MDD participants had lower activation in one cluster covering areas of the right thalamus, right insula, right hippocampus and right superior temporal gyrus compared to HC. These findings are illustrated in Figure 1. No differences were observed between the two groups when examining the happy greater than fear contrast.

MDD and Co-morbid Anxiety: Group Analyses

Group comparisons examining brain activity between MDD with and without comorbid anxiety were conducted. Due to sample size limitations, these comparisons were carried out in the full MDD sample only, not between medicated and unmedicated groups separately. MDD with anxiety disorders and those without did not differ in regards to medication status [$\chi^2(1, N=34)=0.59, p=.044$].

No group differences were found between groups of differing comorbidity status for either the fear greater than happy or happy greater than fear contrast. This suggests that the presence of concurrent, clinical anxiety was not associated with an altered response to fearful or happy facial expressions.

BOLD Response and Depression Severity

Pearson correlation analyses were run to examine how depression severity in the unmedicated MDD sample was related to BOLD response in the cluster that survived thresholding at the group comparison level for the fear greater than happy contrast (right insular/thalamic/hippocampal cluster). BDI scores were available for a subsample (N=19) of the unmedicated MDD group. All scores were demeaned (M=28.05, SD=14.19) prior to analysis. Results (Figure 2) indicate that BOLD percent signal change and BDI scores were not significantly correlated (r (19)=-0.15, p=0.54).

Discussion

A wide body of literature in adults and adolescents suggests that emotional processing abnormalities in depression are related to alterations in fronto-limbic neurocircuitry. This study aimed to expand upon previous findings by comparing differences in brain function in response to fearful and happy faces among clinically depressed and healthy adolescents using fMRI methods.

Areas of the fusiform face area and other supplementary brain regions crucial for face recognition and processing (Haxby et al., 2000; Kanwisher & Yovel, 2006; Platek et al., 2006) showed greater activation to both fearful and happy faces as compared to presentation of a fixation cross in both HC and MDD. In addition, when MDD and HC groups were examined separately, fearful faces elicited greater response in areas of the amygdala than did happy faces. It is important to note, however, that these findings in HC were present to a lesser degree than they were for the MDD group. These data suggest that the emotional faces task used in this study, which has been widely employed in a

variety of forms in previous research, activated expected brain areas and was appropriate for testing the specific hypotheses presented.

Contrary to expectations, however, neither the medicated nor unmedicated MDD groups demonstrated significantly different levels of amygdalar activation compared to controls when viewing fearful faces. These findings oppose those in the adolescent literature that have identified specific alterations in amygdala activity in response to fearful facial stimuli (Beesdo et al., 2009; Monk et al., 2008; Tao et al., 2012; Yang et al., 2010). However, while these studies employed the use of whole brain analyses, amygdalar findings primarily emerged when using a region of interest (ROI) approach. The amygdala is a relatively small brain region, and it is possible that BOLD activity that does exist in this area fails to survive multiple comparison corrections that account for whole brain statistical tests. In addition, slight differences in task presentation may have contributed to the null results observed in this study. Whereas the present study compared happy and fearful faces viewed in conjunction with a neutral target-response task, Tao et al. (2012) compared fear greater than neutral expressions and Beesdo and colleagues (2009) examined amygdala activity while participants actively rated the intensity of the emotional stimulus. Similarly, the paradigm employed by Yang et al (2010) presented each emotional stimulus for several seconds in duration, which would invariably result in a different hemodynamic response than that to stimuli in this study, which were displayed at significantly quicker intervals.

In a review of the adult literature, Stuhrmann (2011) noted that half of the studies that investigated facial emotion processing in major depression failed to yield significant amygdala findings. Of those that did, most compared activation to sad facial stimuli. In

response to the lack of findings following explicitly displayed fearful faces, some researchers have suggested that mood congruent processing bias and associated fronto-limbic dysfunction in MDD may be better measured using sad rather than fearful emotional cues (Arnone et al., 2012).

Additionally, several previous studies that report heightened amygdala activity in MDD included participants with comorbid anxiety (e.g., Victor et al 2010), which has lead Arnone et al. (2012) to suggest that amygdala findings to fear conditions in MDD may be a consequence of diagnostic comorbidity, not depressive symptomatology more specifically. Results from this study do not appear to support this claim. While it was hypothesized that responsivity would be greatest in depressed adolescents with concurrent anxiety, no differences in amygdalar activation were observed between those with and without a comorbid anxiety disorder. However, the present study did not exclude for other types of psychiatric comorbidity, namely Attention Deficit/Hyperactivity Disorder (ADHD) and Oppositional Defiant Disorder (ODD). Both of these illnesses have been associated with fronto-limbic alterations in previous research (Matthys, Vanderschuren, & Schutter, 2012; Posner et al., 2011), so it is possible that examining a diagnostically diverse sample of depressed adolescents in general could have contributed to the lack of amygdala findings between 1) the HC and MDD groups, and 2) the MDD groups with and without comorbid anxiety in this study.

Also contrary to hypotheses were the lack of findings in prefrontal activity between HC and either medicated or unmedicated MDD participants. It was expected that depressed adolescents would demonstrate reduced PFC function to fearful faces, perhaps reflecting a decreased ability to regulate limbic system activation in response to negative

stimuli. According to Stuhrmann et al. (2011), literature on PFC activity in MDD emotion processing is highly inconsistent, where studies have reported increased (Keedwell et al., 2005), decreased (Lawrence et al., 2004), and no differences in activation between patient and control groups. The mixed findings make it difficult to draw firm conclusions regarding the role of prefrontal activity in emotional regulation processing in adolescent MDD; however, it is possible that variations in the degree to which attention and cognitive control are required in emotional face paradigms could contribute to the lack of consistent results (Killgore & Yurgelun-Todd, 2006).

Results from this study do suggest that adolescent MDD is associated with altered activity within other regions of fronto-limbic circuitry. Specifically, depressed adolescents showed reduced activation in areas of the right thalamus, insula and hippocampus when viewing fearful faces, a pattern of findings that has been previously reported by Townsend et al. (2010) in depressed adults. Similarly, when employing an emotional faces task nearly identical to the one presented in this study, Tao et al. (2012) also found alterations in regions of the insula and right hippocampus among depressed adolescents compared to controls when viewing fearful faces. However, authors note that these findings did not survive multiple comparison corrections.

Structural equation and path modeling studies using positron emission tomography in depressed populations indicate that thalamic and limbic regions, such as the hippocampus and insula, possess strong connections with the frontal cortex (e.g., anterior cingulate cortex, orbital frontal cortex) and amygdala (Seminowicz et al., 2004). According to Mayberg's model (Mayberg 1997, 2003), communication between hippocampal/insular regions and neocortical structures is mediated in part by thalamic

activity, where the thalamus serves to relay information between paralimbic and cortical areas (Morgane, Galler, & Mokler, 2005). Meta-analytic results from imaging studies in emotion and cognition indicate that reduced right thalamic activity, specifically, is involved in biased processing of emotional salience and in difficulties with affective switching in MDD (Diener et al., 2012).

In regards to the insula, studies suggest that the structure not only plays a role in the subjective experience of emotion (Suzuki, 2012) but in relaying automatic responses to aversive and threatening stimuli to the amygdala (Ongur & Price, 2000; Phelps et al., 2001). Additionally, the hippocampus has been implicated in the inhibition of both the stress response system and of anxiety to potentially threatening cues in general (Lopez, Akil, & Watson, 1999; McNaughton & Gray, 2000).

Given these findings, it is possible that decreased activity in thalamic and paralimbic regions observed among depressed adolescents in this study reflects deficits in the ability to elicit cognitive control from higher cortical regions and to accurately respond to and process the emotional significance of fearful stimuli respectfully. More research is needed to explain how this might relate to negative emotion processing biases in adolescent MDD more specifically. However, Mayberg (1997) notes that failure in or between any component of the fronto-limbic neural circuit contributes to depressive symptomology. Results from this study suggest that deficits in emotional processing among adolescents with MDD could be a consequence of functional abnormalities within insular, thalamic, and hippocampal regions.

The pattern of observed findings also adds to the literature suggesting that MDD is associated with alterations in functional laterality, where in general, depression has

been found to be associated with a right hemisphere dominance as reflected by right hemisphere hyperactivation and a left hemisphere hypoactivation (Hecht, 2010). However, Diener et al. (2012) noted that subcortical structures appear to show the reverse pattern, where there is reduced right hemisphere activity in depressed samples. In this study, decreased activation in the MDD group was similarly constrained to regions within the right hemisphere. Consistent with the present study, Townsend et al. (2010) found reduced right hemisphere activity in the insula and in medial temporal, occipital, and hippocampal gyri in a sample of unmedicated depressed adults in response to an emotional faces task. Klimes-Dougan et al. (in submission) also identified associations between hypothalamic pituitary adrenal (HPA) function and resting state functional connectivity between fronto-limbic brain regions in the right hemisphere among depressed adolescents compared to controls. Various explanations have been proposed as to the functional importance of this asymmetry. There is evidence to suggest that the left hemisphere is implicated more in processing negative emotions and the right hemisphere is implicated more in processing positive emotions (Townsend et al., 2010); however, these conclusions remain mixed (Alves, Aznar-Casanova, & Fukusima, 2009).

The results of this study provide important information about regions associated with emotion processing in adolescent MDD; however, there are a number of study limitations that should be noted. The most important limitation is the small sample size, which limits the power to consistently detect group differences. In addition, region of interest analyses were not conducted to evaluate amygdala and area-specific prefrontal activity in response to task stimuli. Most studies in adolescent MDD employed the use of this type of analysis, which reduces the number of voxel comparisons being made and

improves the likelihood of observing true statistical differences in activation within small structures. ROI analyses are currently being conducted as a follow-up to the whole-brain approach described here and will hopefully provide further evidence regarding the role of these structures in adolescent MDD. Failing to account for other psychiatric comorbidities (e.g., ADHD) presents another study limitation. Similarly, IQ was significantly lower in the unmedicated MDD group, which was not accounted for during analysis. Although it is unlikely that variations in intellectual ability are associated with performance on a passive viewing task, this potential confound should be evaluated in future steps. Lastly, this study only examined brain function in response to happy and fearful faces. It is possible, as Victor et al. (2010) suggested, that other types of emotional stimuli better elicit fronto-limbic response in adolescents with MDD. Brain activity in response to other emotions will be necessary to further understand the neural correlates of emotion processing in this population.

This study adds to the current literature on emotional face processing in adolescent MDD and provides evidence for specific insular, hippocampal and thalamic deficits in response to fearful stimuli. Findings are consistent with previous research that has failed to identify differences in amygdala activity in unmedicated MDD (Townsend et al., 2010). Results do not support previously proposed hypotheses of hyper amygdala and hypo prefrontal activity in this group. Instead, findings suggest that difficulties in emotion processing and regulation in depressed youth are more associated with abnormalities in secondary subcortical and paralimbic brain regions within the fronto-limbic neural network. To clarify inconsistencies within the literature, future research should examine brain function using larger sample sizes and higher magnet field

strengths. Similarly, longitudinal studies of emotion processing deficits in adolescent MDD are needed in order to better identify whether abnormalities are state or trait dependent. Such information has the potential to advance our understanding of the neurobiological underpinnings of abnormal emotion processing during this critically important developmental period.

References

Alves, N. T., Aznar-Casanova, J. A., & Fukusima, S. S. (2009). Patterns of brain asymmetry in the perception of positive and negative facial expressions. *Laterality, 14*(3), 256-272. doi: 10.1080/13576500802362927; 10.1080/13576500802362927

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (Fourth Edition, Text Revision (DSM-IV-TR) ed.). Arlington, VA:

Arnone, D., McKie, S., Elliott, R., Thomas, E. J., Downey, D., Juhasz, G., . . . Anderson, I. M. (2012). Increased amygdala responses to sad but not fearful faces in major depression: Relation to mood state and pharmacological treatment. *The American Journal of Psychiatry, 169*(8), 841-850. doi: 10.1176/appi.ajp.2012.11121774; 10.1176/appi.ajp.2012.11121774

Bechara, A. (2004). The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. *Brain and Cognition, 55*(1), 30-40. doi: 10.1016/j.bandc.2003.04.001

Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex (New York, N.Y.: 1991), 10*(3), 295-307.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the beck depression inventory-II"*. San Antonio, TX: Psychological Corporation.

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. (1996). Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment, 67*(3), 588-597. doi: 10.1207/s15327752jpa6703_13

Beesdo, K., Lau, J. Y., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., . . . Pine, D. S. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry, 66*(3), 275-285. doi: 10.1001/archgenpsychiatry.2008.545; 10.1001/archgenpsychiatry.2008.545

Berndt, E. R., Koran, L. M., Finkelstein, S. N., Gelenberg, A. J., Kornstein, S. G., Miller, I. M., . . . Keller, M. B. (2000). Lost human capital from early-onset chronic depression. *The American Journal of Psychiatry, 157*(6), 940-947.

Birmaher, B., Arbelaez, C., & Brent, D. (2002). Course and outcome of child and adolescent major depressive disorder. *Child and Adolescent Psychiatric Clinics of North America, 11*(3), 619-37, x.

Bradley, B. P., Mogg, K., & Lee, S. C. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. *Behaviour Research and Therapy, 35*(10), 911-927.

Bradley, B. P., Mogg, K., Millar, N., & White, J. (1995). Selective processing of negative information: Effects of clinical anxiety, concurrent depression, and awareness. *Journal of Abnormal Psychology, 104*(3), 532-536.

Bradley, M. M., Cuthbert, B. N., & Lang, P. J. (1991). Startle and emotion: Lateral acoustic probes and the bilateral blink. *Psychophysiology, 28*(3), 285-295.

Brent, D. A., Kolko, D. J., Birmaher, B., Baugher, M., Bridge, J., Roth, C., & Holder, D. (1998). Predictors of treatment efficacy in a clinical trial of three psychosocial treatments for adolescent depression. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*(9), 906-914. doi: 10.1097/00004583-199809000-00010

Caseras, X., Garner, M., Bradley, B. P., & Mogg, K. (2007). Biases in visual orienting to negative and positive scenes in dysphoria: An eye movement study. *Journal of Abnormal Psychology, 116*(3), 491-497. doi: 10.1037/0021-843X.116.3.491

Cullen, K. R., Gee, D. G., Klimes-Dougan, B., Gabbay, V., Hulvershorn, L., Mueller, B. A., . . . Milham, M. P. (2009). A preliminary study of functional connectivity in comorbid adolescent depression. *Neuroscience Letters, 460*(3), 227-231. doi: 10.1016/j.neulet.2009.05.022

Cullen, K. R., Klimes-Dougan, B., Muetzel, R., Mueller, B. A., Camchong, J., Houri, A., . . . Lim, K. O. (2010). Altered white matter microstructure in adolescents with major depression: A preliminary study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(2), 173-83.e1.

Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *NeuroImage, 61*(3), 677-685. doi: 10.1016/j.neuroimage.2012.04.005; 10.1016/j.neuroimage.2012.04.005

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. *Brain Structure & Function, 213*(1-2), 93-118. doi: 10.1007/s00429-008-0189-x

Eizenman, M., Yu, L. H., Grupp, L., Eizenman, E., Ellenbogen, M., Gemar, M., & Levitan, R. D. (2003). A naturalistic visual scanning approach to assess selective attention in major depressive disorder. *Psychiatry Research, 118*(2), 117-128.

Ekman, P., & Friesen, W. (1976). *Pictures of facial affect.* . Palo Alto, CA: Consulting Psychologist Press.

Fitzgerald, D. A., Angstadt, M., Jelsone, L. M., Nathan, P. J., & Phan, K. L. (2006). Beyond threat: Amygdala reactivity across multiple expressions of facial affect. *NeuroImage, 30*(4), 1441-1448. doi: 10.1016/j.neuroimage.2005.11.003

Foland-Ross, L. C., & Gotlib, I. H. (2012a). Cognitive and neural aspects of information processing in major depressive disorder: An integrative perspective. *Frontiers in Psychology, 3*, 489. doi: 10.3389/fpsyg.2012.00489; 10.3389/fpsyg.2012.00489

Foland-Ross, L. C., & Gotlib, I. H. (2012b). Cognitive and neural aspects of information processing in major depressive disorder: An integrative perspective. *Frontiers in Psychology, 3*, 489. doi: 10.3389/fpsyg.2012.00489; 10.3389/fpsyg.2012.00489

Fritzsche, A., Dahme, B., Gotlib, I. H., Joormann, J., Magnussen, H., Watz, H., . . . von Leupoldt, A. (2010). Specificity of cognitive biases in patients with current depression and remitted

depression and in patients with asthma. *Psychological Medicine, 40*(5), 815-826. doi: 10.1017/S0033291709990948; 10.1017/S0033291709990948

Fu, C. H., Williams, S. C., Cleare, A. J., Brammer, M. J., Walsh, N. D., Kim, J., . . . Bullmore, E. T. (2004). 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, 61*(9), 877-889. doi: 10.1001/archpsyc.61.9.877

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., . . . Politi, P. (2009). Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry & Neuroscience : JPN, 34*(6), 418-432.

Gilboa-Schechtman, E., Erhard-Weiss, D., & Jeczemien, P. (2002). Interpersonal deficits meet cognitive biases: Memory for facial expressions in depressed and anxious men and women. *Psychiatry Research, 113*(3), 279-293.

Gollan, J., Raffety, B., Gortner, E., & Dobson, K. (2005). Course profiles of early- and adult-onset depression. *Journal of Affective Disorders, 86*(1), 81-86. doi: 10.1016/j.jad.2004.12.009

Gotlib, I. H., Krasnoperova, E., Yue, D. N., & Joormann, J. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of Abnormal Psychology, 113*(1), 121-135. doi: 10.1037/0021-843X.113.1.121

Greenberg, P. E., Kessler, R. C., Birnbaum, H. G., Leong, S. A., Lowe, S. W., Berglund, P. A., & Corey-Lisle, P. K. (2003). The economic burden of depression in the united states: How did it change between 1990 and 2000? *The Journal of Clinical Psychiatry, 64*(12), 1465-1475.

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology, 21*(4), 424-430. doi: 10.1097/WCO.0b013e328306f2c5

Halari, R., Simic, M., Pariante, C. M., Papadopoulos, A., Cleare, A., Brammer, M., . . . Rubia, K. (2009). Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naive adolescents with depression compared to controls. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 50*(3), 307-316. doi: 10.1111/j.1469-7610.2008.01972.x; 10.1111/j.1469-7610.2008.01972.x

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*(6), 223-233.

Hecht, D. (2010). Depression and the hyperactive right-hemisphere. *Neuroscience Research, 68*(2), 77-87. doi: 10.1016/j.neures.2010.06.013; 10.1016/j.neures.2010.06.013

Hirschfeld, R. M. (2012). The epidemiology of depression and the evolution of treatment. *The Journal of Clinical Psychiatry, 73 Suppl 1*, 5-9. doi: 10.4088/JCP.11096su1c.01; 10.4088/JCP.11096su1c.01

Hollon, S. D., Shelton, R. C., Wisniewski, S., Warden, D., Biggs, M. M., Friedman, E. S., . . . Rush, A. J. (2006). Presenting characteristics of depressed outpatients as a function of recurrence: Preliminary findings from the STAR*D clinical trial. *Journal of Psychiatric Research, 40*(1), 59-69. doi: 10.1016/j.jpsychires.2005.07.008

Joormann, J., Siemer, M., & Gotlib, I. H. (2007). Mood regulation in depression: Differential effects of distraction and recall of happy memories on sad mood. *Journal of Abnormal Psychology, 116*(3), 484-490. doi: 10.1037/0021-843X.116.3.484

Joormann, J., Talbot, L., & Gotlib, I. H. (2007). Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology, 116*(1), 135-143. doi: 10.1037/0021-843X.116.1.135

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. *Philosophical Transactions of the Royal Society of London.Series B, Biological Sciences, 361*(1476), 2109-2128. doi: 10.1098/rstb.2006.1934

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*(7), 980-988. doi: 10.1097/00004583-199707000-00021

Keedwell, P. A., Andrew, C., Williams, S. C., Brammer, M. J., & Phillips, M. L. (2005). A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. *Biological Psychiatry, 58*(6), 495-503. doi: 10.1016/j.biopsych.2005.04.035

Keller, M. B., Lavori, P. W., Mueller, T. I., Endicott, J., Coryell, W., Hirschfeld, R. M., & Shea, T. (1992). Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry, 49*(10), 809-816.

Kessler, R. C. (2012). The costs of depression. *The Psychiatric Clinics of North America, 35*(1), 1-14. doi: 10.1016/j.psc.2011.11.005; 10.1016/j.psc.2011.11.005

Kessler, R. C., Avenevoli, S., & Ries Merikangas, K. (2001). Mood disorders in children and adolescents: An epidemiologic perspective. *Biological Psychiatry, 49*(12), 1002-1014.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., . . . National Comorbidity Survey Replication. (2003). The epidemiology of major depressive disorder: Results from the national comorbidity survey replication (NCS-R). *JAMA : The Journal of the American Medical Association, 289*(23), 3095-3105. doi: 10.1001/jama.289.23.3095

Kessler, R. C., Birnbaum, H., Bromet, E., Hwang, I., Sampson, N., & Shahly, V. (2010). Age differences in major depression: Results from the national comorbidity survey replication (NCS-R). *Psychological Medicine, 40*(2), 225-237. doi: 10.1017/S0033291709990213; 10.1017/S0033291709990213

Killgore, W. D., & Yurgelun-Todd, D. A. (2006). Ventromedial prefrontal activity correlates with depressed mood in adolescent children. *Neuroreport, 17*(2), 167-171.

Koster, A., Bosma, H., Kempen, G. I., Penninx, B. W., Beekman, A. T., Deeg, D. J., & van Eijk, J. T. (2006). Socioeconomic differences in incident depression in older adults: The role of psychosocial factors, physical health status, and behavioral factors. *Journal of Psychosomatic Research, 61*(5), 619-627. doi: 10.1016/j.jpsychores.2006.05.009

Kujawa, A. J., Torpey, D., Kim, J., Hajcak, G., Rose, S., Gotlib, I. H., & Klein, D. N. (2011). Attentional biases for emotional faces in young children of mothers with chronic or recurrent depression. *Journal of Abnormal Child Psychology, 39*(1), 125-135. doi: 10.1007/s10802-010-9438-6; 10.1007/s10802-010-9438-6

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review, 97*(3), 377-395.

Lawrence, N. S., Williams, A. M., Surguladze, S., Giampietro, V., Brammer, M. J., Andrew, C., . . . Phillips, M. L. (2004). Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biological Psychiatry, 55*(6), 578-587. doi: 10.1016/j.biopsych.2003.11.017

Lawson, C., MacLeod, C., & Hammond, G. (2002). Interpretation revealed in the blink of an eye: Depressive bias in the resolution of ambiguity. *Journal of Abnormal Psychology, 111*(2), 321-328.

Lenroot, R. K., & Giedd, J. N. (2006). Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews, 30*(6), 718-729. doi: 10.1016/j.neubiorev.2006.06.001

Lewinsohn, P. M., Allen, N. B., Seeley, J. R., & Gotlib, I. H. (1999). First onset versus recurrence of depression: Differential processes of psychosocial risk. *Journal of Abnormal Psychology, 108*(3), 483-489.

Lim, S. L., & Kim, J. H. (2005). Cognitive processing of emotional information in depression, panic, and somatoform disorder. *Journal of Abnormal Psychology, 114*(1), 50-61. doi: 10.1037/0021-843X.114.1.50

Lopez, J. F., Akil, H., & Watson, S. J. (1999). Neural circuits mediating stress. *Biological Psychiatry, 46*(11), 1461-1471.

Lopez-Leon, S., Janssens, A. C., Gonzalez-Zuloeta Ladd, A. M., Del-Favero, J., Claes, S. J., Oostra, B. A., & van Duijn, C. M. (2008). Meta-analyses of genetic studies on major depressive disorder. *Molecular Psychiatry, 13*(8), 772-785. doi: 10.1038/sj.mp.4002088

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*, 167-195. doi: 10.1146/annurev.clinpsy.1.102803.143916

Mathews, A., Ridgeway, V., & Williamson, D. A. (1996). Evidence for attention to threatening stimuli in depression. *Behaviour Research and Therapy, 34*(9), 695-705.

Matthys, W., Vanderschuren, L. J., & Schutter, D. J. (2012). The neurobiology of oppositional defiant disorder and conduct disorder: Altered functioning in three mental domains. *Development and Psychopathology,* , 1-15. doi: 10.1017/S0954579412000272

Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences, 9*(3), 471-481.

Mayberg, H. S. (2003). Modulating dysfunctional limbic-cortical circuits in depression: Towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin, 65*, 193-207.

McNaughton, N., & Gray, J. A. (2000). Anxiolytic action on the behavioural inhibition system implies multiple types of arousal contribute to anxiety. *Journal of Affective Disorders, 61*(3), 161-176.

Merikangas, K. R., He, J. P., Burstein, M., Swendsen, J., Avenevoli, S., Case, B., . . . Olfson, M. (2011). Service utilization for lifetime mental disorders in U.S. adolescents: Results of the national comorbidity survey-adolescent supplement (NCS-A). *Journal of the American*

Academy of Child and Adolescent Psychiatry, 50(1), 32-45. doi: 10.1016/j.jaac.2010.10.006; 10.1016/j.jaac.2010.10.006

Mogg, K., Bradley, B. P., & Williams, R. (1995). Attentional bias in anxiety and depression: The role of awareness. *The British Journal of Clinical Psychology / the British Psychological Society, 34 (Pt 1)*(Pt 1), 17-36.

Monk, C. S., Klein, R. G., Telzer, E. H., Schroth, E. A., Mannuzza, S., Moulton, J. L.,3rd, . . . Ernst, M. (2008). Amygdala and nucleus accumbens activation to emotional facial expressions in children and adolescents at risk for major depression. *The American Journal of Psychiatry, 165*(1), 90-98. doi: 10.1176/appi.ajp.2007.06111917

Monroe, S. M., Rohde, P., Seeley, J. R., & Lewinsohn, P. M. (1999). Life events and depression in adolescence: Relationship loss as a prospective risk factor for first onset of major depressive disorder. *Journal of Abnormal Psychology, 108*(4), 606-614.

Morgane, P. J., Galler, J. R., & Mokler, D. J. (2005). A review of systems and networks of the limbic forebrain/limbic midbrain. *Progress in Neurobiology, 75*(2), 143-160. doi: 10.1016/j.pneurobio.2005.01.001

Nes, R. B., Czajkowski, N. O., Roysamb, E., Orstavik, R. E., Tambs, K., & Reichborn-Kjennerud, T. (2013). Major depression and life satisfaction: A population-based twin study. *Journal of Affective Disorders, 144*(1-2), 51-58. doi: 10.1016/j.jad.2012.05.060; 10.1016/j.jad.2012.05.060

Ongur, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex (New York, N.Y.: 1991), 10*(3), 206-219.

Peluso, M. A., Glahn, D. C., Matsuo, K., Monkul, E. S., Najt, P., Zamarripa, F., . . . Soares, J. C. (2009). Amygdala hyperactivation in untreated depressed individuals. *Psychiatry Research, 173*(2), 158-161. doi: 10.1016/j.pscychresns.2009.03.006; 10.1016/j.pscychresns.2009.03.006

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Gore, J. C., Grillon, C., & Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nature Neuroscience, 4*(4), 437-441. doi: 10.1038/86110

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry, 54*(5), 515-528.

Platek, S. M., Loughead, J. W., Gur, R. C., Busch, S., Ruparel, K., Phend, N., . . . Langleben, D. D. (2006). Neural substrates for functionally discriminating self-face from personally familiar faces. *Human Brain Mapping, 27*(2), 91-98. doi: 10.1002/hbm.20168

Posner, J., Nagel, B. J., Maia, T. V., Mechling, A., Oh, M., Wang, Z., & Peterson, B. S. (2011). Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(8), 828-37.e3. doi: 10.1016/j.jaac.2011.05.010; 10.1016/j.jaac.2011.05.010

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 35*(1), 192-216. doi: 10.1038/npp.2009.104

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences, 16*(1), 61-71. doi: 10.1016/j.tics.2011.12.011; 10.1016/j.tics.2011.12.011

Romeo, R. D., & McEwen, B. S. (2006). Stress and the adolescent brain. *Annals of the New York Academy of Sciences, 1094*, 202-214. doi: 10.1196/annals.1376.022

Savitz, J., & Drevets, W. C. (2009). Bipolar and major depressive disorder: Neuroimaging the developmental-degenerative divide. *Neuroscience and Biobehavioral Reviews, 33*(5), 699-771. doi: 10.1016/j.neubiorev.2009.01.004

Seminowicz, D. A., Mayberg, H. S., McIntosh, A. R., Goldapple, K., Kennedy, S., Segal, Z., & Rafi-Tari, S. (2004). Limbic-frontal circuitry in major depression: A path modeling metanalysis. *NeuroImage, 22*(1), 409-418. doi: 10.1016/j.neuroimage.2004.01.015

Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: An fMRI study. *Biological Psychiatry, 50*(9), 651-658.

Simon, R. I., & Hales, R. E. (Eds.). (2006). *Suicide risk: Assessing the unpredictable.* (1st edition ed.). Arlington,VA: American Psychiatric Publishing, Inc.

Steingard, R. J., Renshaw, P. F., Hennen, J., Lenox, M., Cintron, C. B., Young, A. D., . . . Yurgelun-Todd, D. A. (2002). Smaller frontal lobe white matter volumes in depressed adolescents. *Biological Psychiatry, 52*(5), 413-417.

Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in major depression: A systematic review of neuroimaging findings. *Biology of Mood & Anxiety Disorders, 1*(1), 10-5380-1-10. doi: 10.1186/2045-5380-1-10; 10.1186/2045-5380-1-10

Surguladze, S., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., . . . Phillips, M. L. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological Psychiatry, 57*(3), 201-209. doi: 10.1016/j.biopsych.2004.10.028

Surguladze, S. A., El-Hage, W., Dalgleish, T., Radua, J., Gohier, B., & Phillips, M. L. (2010). Depression is associated with increased sensitivity to signals of disgust: A functional magnetic resonance imaging study. *Journal of Psychiatric Research, 44*(14), 894-902. doi: 10.1016/j.jpsychires.2010.02.010; 10.1016/j.jpsychires.2010.02.010

Suslow, T., Konrad, C., Kugel, H., Rumstadt, D., Zwitserlood, P., Schoning, S., . . . Dannlowski, U. (2010). Automatic mood-congruent amygdala responses to masked facial expressions in

major depression. *Biological Psychiatry, 67*(2), 155-160. doi: 10.1016/j.biopsych.2009.07.023; 10.1016/j.biopsych.2009.07.023

Suzuki, A. (2012). Emotional functions of the insula. *Brain and Nerve = Shinkei Kenkyu no Shinpo, 64*(10), 1103-1112.

Tanti, A., & Belzung, C. (2010a). Open questions in current models of antidepressant action. *British Journal of Pharmacology, 159*(6), 1187-1200. doi: 10.1111/j.1476-5381.2009.00585.x; 10.1111/j.1476-5381.2009.00585.x

Tanti, A., & Belzung, C. (2010b). Open questions in current models of antidepressant action. *British Journal of Pharmacology, 159*(6), 1187-1200. doi: 10.1111/j.1476-5381.2009.00585.x; 10.1111/j.1476-5381.2009.00585.x

Tao, R., Calley, C. S., Hart, J., Mayes, T. L., Nakonezny, P. A., Lu, H., . . . Emslie, G. J. (2012). Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. *The American Journal of Psychiatry, 169*(4), 381-388. doi: 10.1176/appi.ajp.2011.11040615; 10.1176/appi.ajp.2011.11040615

Townsend, J. D., Eberhart, N. K., Bookheimer, S. Y., Eisenberger, N. I., Foland-Ross, L. C., Cook, I. A., . . . Altshuler, L. L. (2010). fMRI activation in the amygdala and the orbitofrontal cortex in unmedicated subjects with major depressive disorder. *Psychiatry Research, 183*(3), 209-217. doi: 10.1016/j.pscychresns.2010.06.001; 10.1016/j.pscychresns.2010.06.001

Victor, T. A., Furey, M. L., Fromm, S. J., Ohman, A., & Drevets, W. C. (2010). Relationship between amygdala responses to masked faces and mood state and treatment in major depressive disorder. *Archives of General Psychiatry, 67*(11), 1128-1138. doi: 10.1001/archgenpsychiatry.2010.144; 10.1001/archgenpsychiatry.2010.144

Watkins, P. C., Martin, C. K., & Stern, L. D. (2000). Unconscious memory bias in depression: Perceptual and conceptual processes. *Journal of Abnormal Psychology, 109*(2), 282-289.

Wechsler, D. (1999). In The Psychological Corporation (Ed.), *Wechsler abbreviated scale of intelligence.* . New York, NY.: Harcourt Brace & Company.

Wicker, B., Keysers, C., Plailly, J., Royet, J. P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in my insula: The common neural basis of seeing and feeling disgust. *Neuron, 40*(3), 655-664.

Widom, C. S., DuMont, K., & Czaja, S. J. (2007). A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Archives of General Psychiatry, 64*(1), 49-56. doi: 10.1001/archpsyc.64.1.49

Wolfensberger, S. P., Veltman, D. J., Hoogendijk, W. J., Boomsma, D. I., & de Geus, E. J. (2008). Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. *NeuroImage, 41*(2), 544-552. doi: 10.1016/j.neuroimage.2008.01.053; 10.1016/j.neuroimage.2008.01.053

World Health Organization (WHO). (2008). *The global burden of disease update.* (). Geneva, Switzerland: WHO Press.

Yang, T. T., Simmons, A. N., Matthews, S. C., Tapert, S. F., Frank, G. K., Max, J. E., . . . Paulus, M. P. (2010). Adolescents with major depression demonstrate increased amygdala activation. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(1), 42-51.

Zhong, M., Wang, X., Xiao, J., Yi, J., Zhu, X., Liao, J., . . . Yao, S. (2011). Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biological Psychology, 88*(2-3), 233-242. doi: 10.1016/j.biopsycho.2011.08.007; 10.1016/j.biopsycho.2011.08.007

Zisook, S., Lesser, I., Stewart, J. W., Wisniewski, S. R., Balasubramani, G. K., Fava, M., . . . Rush, A. J. (2007). Effect of age at onset on the course of major depressive disorder. *The American Journal of Psychiatry, 164*(10), 1539-1546. doi: 10.1176/appi.ajp.2007.06101757

Table 1. Demographic and clinical data for the full sample.

		HC (*N*=16)		Medicated MDD (*N*=12)		Unmedicated MDD (*N*=22)			
		M	***SD***	***M***	***SD***	***M***	***SD***	***F***	***p***
Age (years)		15.98	2.28	16.23	1.05	15.42	1.93	0.82	0.45
IQ[a]		113.81	11.44	114.17	11.62	98.95	16.43	7.15	**0.002**
BDI[*,b]		3.71	3.04	23.50	13.07	28.05	14.19	9.75	**0.001**
		N	***%***	***N***	***%***	***N***	***%***	χ^2	***p***
Gender	*Male*	5	31.3	3	25.0	3	13.6	1.76	0.42
	Female	11	68.8	9	75.0	19	86.4		
Race	*Caucasian*	11	68.8	9	75.0	16	72.7	5.88[†]	1.00
	AA	0	0.0	0	0.0	2	9.1		
	Asian	1	6.2	0	0.0	1	4.6		
	NA	0	0.0	1	8.3	0	0.0		
	Biracial	4	25.0	2	16.7	3	13.6		
Handedness	*Right*	14	87.5	12	100.0	20	90.9	1.52	0.36
	Left	2	12.5	0	0.0	2	9.1		
Co-morbidity	Any Dx			8	66.6	12	54.5	0.40	0.84
	GAD			4	33.3	6	27.3		
	SAD			1	8.3	2	9.1		
	PTSD			1	8.3	1	4.6		
	OCD			1	8.3	1	4.6		
	SP			1	8.3	--	--		
	ADHD			2	16.7	4	18.1		
	ODD			--	--	2	9.1		
	DYS			--	--	2	9.1		

HC=Healthy Controls, MDD=Major Depression, AA=African American, NA=Native American, Any Dx= Any co-morbid diagnosis reported. GAD=Generalized Anxiety Disorder, SAD=Social Anxiety Disorder, PTSD=Posttraumatic Stress Disorder, OCD=Obsessive Compulsive Disorder, SP=Specific Phobia, ADHD=Attention Deficit-Hyperactivity Disorder, ODD=Oppositional Defiant Disorder, DYS=Dysthymia

[a] Unmedicated MDD significantly lower than HC (p<0.01) and Medicated MDD (p<0.05*);* [b] Unmedicated MDD (p<0.01) and Medicated MDD (p<0.05*)* significantly higher than HC

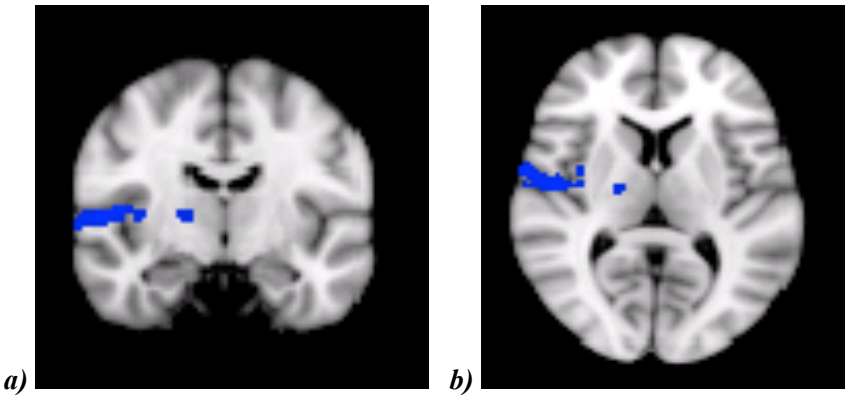
[*] BDI based on a subsample of participants: HC (*N*=7), Medicated MDD (*N*=6), Unmedicated (*N*=19)

Table 2. Anatomical location and z-score associated with peak activation of significant clusters observed between HC (*N*=16) and the full MDD sample (*N*=34)

Contrast	Anatomical Location	MNI Coordinates (mm)			z-score	Cluster (voxels)
		X	Y	Z		
MDD						
Fear > +	Posterior cingulate gyrus	16	-28	26	4.64	9222***
	L temporal occipital fusiform cortex	-32	-54	-18	5.6	1673***
	R temporal occipital fusiform cortex	40	-62	-22	5.47	1934***
	R frontal pole	34	50	4	3.9	1545***
Happy > +	L temporal occipital fusiform cortex	-34	-54	-18	5.45	5041***
	R temporal occipital fusiform cortex	36	-58	-20	4.66	6945***
	Anterior cingulate gyrus/paracingulate gyrus	4	44	2	4.25	876**
Fear > Happy	L temporal fusiform cortex, middle temporal gyrus, insula cortex, amygdala, hippocampus	-44	-18	-20	4.32	4747***
	L nucleus accumbens, anterior cingulate cortex	-8	22	-2	4.35	1342***
	L medial orbital frontal cortex	-26	52	-16	4.31	868**
	L superior parietal cortex	-24	-44	46	5.31	1938***
	R superior parietal cortex	24	-45	50	4.65	2008***
HC						
Fear > +	R supramarginal gyrus	60	-24	32	4.67	5213**
	L temporal occipital fusiform cortex	-36	-56	-18	4.66	1971**
	R occipital fusiform cortex	36	-60	18	5.17	1100***
	L parietal operculum cortex	-50	-38	28	3.47	723**
Happy > +	R temporal occipital fusiform cortex	36	-60	-18	4.21	4401***
	L parietal operculum cortex	-40	-34	26	3.78	1737***
	L temporal occipital fusiform cortex	-36	-54	-18	4.08	526*

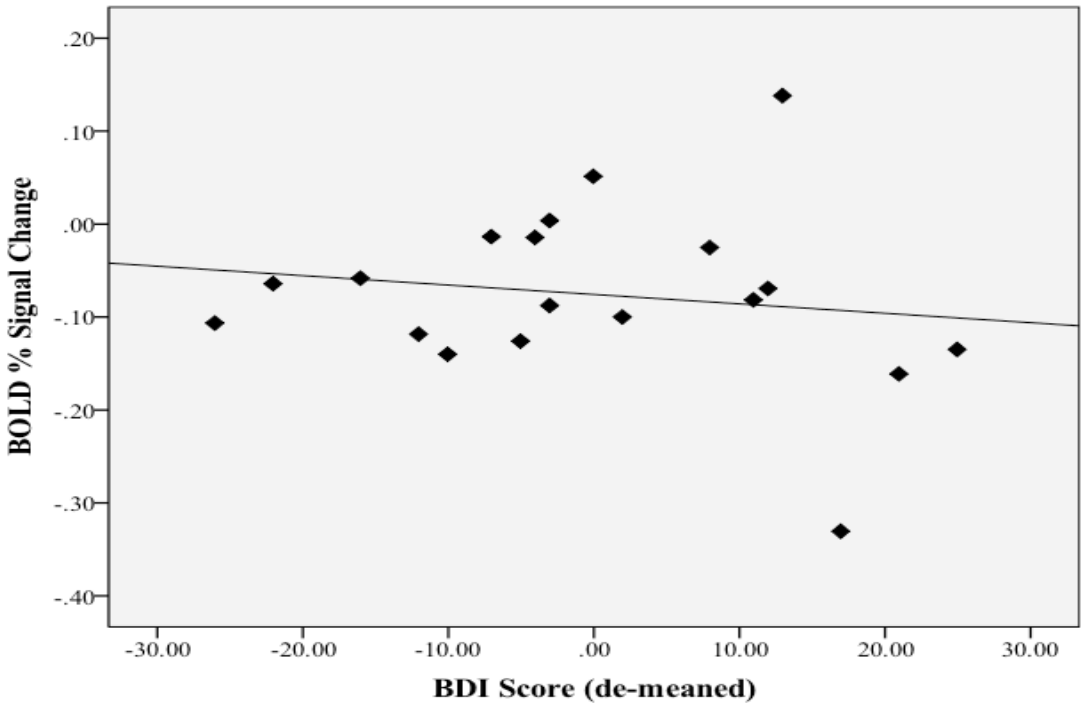
Findings based on initial z threshold value = 2.32; clusters corrected for multiple comparisons
R=right hemisphere, L=left hemisphere, +=fixation cross
*p<0.05, **p<0.01, ***p<0.001

Figure 1.



Areas in right hemisphere (depicted via a (a) coronal slice and (b) axial slice) that showed decreased activation in unmedicated MDD participants compared to healthy controls in response to the fearful > happy contrast. Cluster (664 voxels) contains regions of the right hippocampus (MNI coordinates: x=32, y=-38, z=-8), right thalamus (x=6, y=-18, z=2), and right insula (x=38, y=-10, z=6). Voxels exceeded initial threshold, z = 2.32, and survived multiple comparison correction, $p<0.05$.

Figure 2.



Scatterplot depicting nonsignifanct correlation (r (19)=-0.15, p=0.54) between BOLD percent signal change and depression severity score (group-centered BDI) in a subsample of the unmedicated MDD group (N=19). Percent signal change was measured in the cluster (MNI coordinates: x=32, y=-38, z=-8) that survived statistical thresholding at the group