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Altered Neural Function to Happy Faces in Adolescents with and at Risk for Depression

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Abstract

Background—There is accumulating evidence of alterations in neural circuitry underlying the processing of social-affective information in adolescent Major Depressive Disorder (MDD). However the extent to which such alterations are present in youth at risk for mood disorders remains unclear.

Method—Whole-brain blood oxygenation level-dependent task responses and functional connectivity using generalized psychophysiological interaction (gPPI) analyses to mild and intense happy face stimuli was examined in 29 adolescents with MDD (MDD; M age, 16.0, SD 1.2 years), 38 healthy adolescents at risk of a mood disorder, by virtue of having a parent diagnosed with either Bipolar Disorder (BD) or MDD (Mood-risk; M age 13.4, SD 2.5 years) and 43 healthy control adolescents, having parents with no psychiatric disorder (HC; M age 14.6, SD 2.2 years).

Results—Relative to HC adolescents, Mood-risk adolescents showed elevated right dorsolateral prefrontal cortex (DLPFC) activation to 100% intensity happy (vs. neutral) faces and concomitant lowered ventral putamen activity to 50% intensity happy (vs. neutral) faces. gPPI analyses revealed that MDD adolescents showed significantly lower right DLPFC functional connectivity with the ventrolateral PFC (VLPFC) compared to HC to all happy faces.

Limitations—The current study is limited by the smaller number of healthy offspring at risk for MDD compared to BD.

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Conflicts of Interest

Dr. Birmaher receives royalties for books from Random House, UpToDate and APA Press. Dr. Brent receives royalties from Guilford Press, royalties from the electronic self-rated version of the C-SSRS from ERT, Inc., and royalties from performing duties as an UpToDate Psychiatry Section Editor.

Conclusions—Because Mood-risk adolescents were healthy at the time of the scan, elevated DLPFC and lowered ventral striatal activity in Mood-risk adolescents may be associated with risk or resiliency. In contrast, altered DLPFC-VLPFC functional connectivity in MDD adolescents may be associated with depressed mood state. Such alterations may affect social-affective development and progression to a mood disorder in Mood-risk adolescents. Future longitudinal follow-up studies are needed to directly answer this research question.

Keywords

adolescence; major depressive disorder; social-affective processing; functional connectivity

1. INTRODUCTION

Early adolescence, with the onset of puberty, is a vulnerable developmental period for the onset of mood disorders including Major Depressive Disorder (MDD) (Kessler, 2012; Kessler and Walters, 1998). Adolescent-onset MDD is the most prevalent and debilitating mental illness in adolescence; it is associated with greater symptom severity (compared to adult-onset MDD), recurrent illness through adulthood, and suicidality across the life span (Birmaher et al., 2007; Hollon et al., 2006; Jamison et al., 2006). The fact that most episodes of depression emerge during early adolescence through to early adulthood underscores the importance of research focusing on this developmental period, particularly in youth at risk for MDD.

In addition to a cascade of hormonal (e.g., onset of puberty and rise in levels of sex hormones) and neural (e.g., maturation of reward neural circuitry) changes occurring across the adolescent period, are substantial changes in social-affective development (Blakemore, 2008; Choudhury et al., 2006). Changes in social skills (e.g., increased perspective-taking abilities) and motivational and emotional aspects of social processing (e.g., increased salience of social acceptance and rejection), become increasingly important as adolescents seek potential peer interactions and peer acceptance (Crone and Dahl, 2012). The processing of emotionally salient social cues such as facial expressions, for example, undergo important developmental changes and gain emotional saliency throughout adolescence (Crone and Dahl, 2012; Scherf et al., 2012; Thomas et al., 2007). Accumulating evidence shows alterations in the functioning of frontal, cingulate and limbic neural regions underlying the processing of social-affective information across several mood disorders in adolescence including MDD (Hall et al., 2014; Henderson et al., 2014; Henje Blom et al., 2015; Ho et al., 2014b; Mingtian et al., 2012; Pan et al., 2013; Roberson-Nay et al., 2006; Tao et al., 2012), Bipolar Disorder (BD) (Brotman et al., 2010; Deveney et al., 2014; Diler et al., 2013; Olsavsky et al., 2012; Passarotti et al., 2011; Pavuluri et al., 2007) and youths with severe mood dysregulation (Brotman et al., 2010; Thomas et al., 2012). This suggests that alterations in social-affective processing and their neural correlates may be crucial to understanding vulnerability to mood disorders in adolescents (Blakemore, 2008; Burnett et al., 2011; Crone and Dahl, 2012). However, it is unclear the extent to which such alterations in neural activity underlying emotion processing – particularly to cues of social reward – are present in youth at risk for mood disorders.

A core feature of adolescent MDD is reduced positive affect (Forbes et al., 2004) and reward-seeking behaviors (Forbes et al., 2007; Jazbec et al., 2005). To date, neuroimaging studies of adolescent MDD have examined reward processing in the context of monetary reward. These studies have predominantly reported diminished striatal response during the anticipation and receipt of reward in adolescents with MDD (Forbes et al., 2010; Olino et al., 2011; Shad et al., 2011). Given that emotional facial expressions are socially relevant stimuli and that positive (i.e., happy) emotional facial expressions are perceived as cues of potential social reward in adolescents, it is therefore possible that happy face stimuli would be associated with alterations in neural systems supporting social-affective processing and the regulation of social-affective processes, in adolescents with mood disorders. However only a few studies have examined the neural correlates of positive emotional stimuli in adolescents with MDD (Barch et al., 2012; Hall et al., 2014; Henje Blom et al., 2015; Ho et al., 2014b; Yang et al., 2010), with an overwhelming focus on negative emotional face processing (Barch et al., 2012; Hall et al., 2014; Henderson et al., 2014; Ho et al., 2014a; Matthews et al., 2008; Mingtian et al., 2012; Pan et al., 2013; Roberson-Nay et al., 2006; Tao et al., 2012; Thomas et al., 2001). Of the available studies examining neural responses to positive emotional stimuli, both implicit (e.g., labeling the gender of a an emotional face) and explicit (e.g., labeling the emotion of a facial expression) emotion processing tasks have been used. Across these studies, increased amygdala activation and connectivity to happy faces has been reported in MDD adolescents compared to healthy adolescents (Henje Blom et al., 2015; Yang et al., 2010). Abnormalities in frontal regions have been most consistently reported for medial parts of the PFC and cingulate cortex (both anterior and posterior cingulate) (Henje Blom et al., 2015; Ho et al., 2014b), with some evidence implicating increased connectivity of lateral PFC regions (Henje Blom et al., 2015) in adolescent MDD. Overall however, the evidence has been inconsistent, and some studies have reported no differences in neural activation during the processing of happy faces in depressed adolescents compared to healthy adolescents (Barch et al., 2012; Hall et al., 2014).

Deficits in emotion face processing have also been found in youth at familial risk for mood disorders, namely MDD and BD (Brotman et al., 2008b; Glahn et al., 2010; Joormann et al., 2010). A growing number of fMRI studies in youth at risk for MDD and BD show evidence of alterations in limbic/subcortical (i.e., amygdala, nucleus accumbens) and lateral prefrontal (i.e., DLPFC, ventrolateral PFC; VLPFC) regions during the processing of emotional face stimuli (Brotman et al., 2014; Garrett et al., 2015; Ladouceur et al., 2013; Manelis et al., 2015; Mannie et al., 2011; Monk et al., 2008; Olsavsky et al., 2012; Tseng et al., 2015; Zhong et al., 2011), although only five of these studies explicitly examined happy face stimuli (Brotman et al., 2014; Ladouceur et al., 2013; Manelis et al., 2015; Monk et al., 2008; Olsavsky et al., 2012). In a sample of 10–18 year old healthy offspring at risk for MDD (at risk by virtue of having at least one parent diagnosed with MDD), Monk et al (2008) reported reduced nucleus accumbens activation but elevated amygdala activation during the processing of happy faces in the at-risk youth compared to low-risk youth. In a study by Brotman and colleagues (2014) examining neural activity to morphed emotional (happy, angry) faces during implicit and explicit emotion ratings, youth with and at risk of BD showed decreased modulation of the VLPFC as a function of increasing intensity of happy faces. Of note, this finding was sensitive to task demands and only occurred during

explicit ratings of the faces. In another study, Ladouceur and colleagues (2013) used fMRI functional connectivity methods to examine activity and connectivity in a sample of 8–17 year old healthy offspring having a parent diagnosed with BD, during the performance of a working memory task with emotional face distracters (Ladouceur et al., 2013). This study reported that offspring at risk for BD showed elevated VLPFC activation and concurrent reduced VLPFC functional connectivity with the amygdala and DLPFC during the cognitive task when happy face distracter stimuli were present (Ladouceur et al., 2013). In contrast, a recent study using an implicit dynamic faces task, found elevated right VLPFC-amygdala functional connectivity to happy faces in youths at risk of Bipolar Disorder compared to youths at risk of non-BD psychopathology and healthy youths at low-risk of psychopathology (Manelis et al., 2015). However not all youths at risk of Bipolar Disorder were healthy at the time of the scan, with 11 of the 29 youths having a psychiatric diagnosis, and 5 of the 29 youths being treated with psychotropic medications (Manelis et al., 2015).

Although methodologically different, taken together these studies suggest that such alterations in regions subserving social-affective processing and the higher-order regulation of social-affective processing may render healthy adolescents who are already at risk for a mood disorder, more vulnerable to developing a mood disorder. Conversely, such alterations could act as a resilience factor for the development of MDD. That is, in youth at risk for mood disorders, hyperactivity of lateral PFC regions (compared to both healthy adolescents and adolescents with MDD) to cues of social reward, may reflect compensatory activation in an effort to help prevent the development of MDD. Given that adolescents become more sensitive to reward and social cues such as happy faces that signal the potential for peer interactions, elevated DLPFC and VLPFC activation may reflect increased allocation of attentional resources to happy faces, which is more pronounced in youth at risk of mood disorders. Elevated activation in limbic (Manelis et al., 2015; Olsavsky et al., 2012) and subcortical (Monk et al., 2008) regions to happy faces that has been reported in at risk populations (albeit more consistently for youths at risk for BD), may reflect enhanced reward sensitivity, that is further enforced by hyperconnectivity between lateral PFC and limbic/subcortical regions (Manelis et al., 2015). Conversely, if lateral PFC regions ‘burn out’ and become hypoactive, and functional connectivity with limbic regions is subsequently altered, this may render adolescents unable to regulate responses to social-affective stimuli. In the context of social-affective development, this may be expected to be associated with changes in social-affective behavior such as increased social withdrawal and isolation, and in some cases, the development of MDD.

The aim of our study was to use fMRI to examine neural activity and functional connectivity during the processing of happy faces (vs. neutral) in a large sample of adolescents with MDD, healthy offspring at high familial risk for mood disorders, by virtue of having a parent diagnosed with either MDD or BD, and healthy offspring at low familial risk for mood disorders, by virtue of having parents and first-degree relatives with no history of psychiatric diagnoses. Our focus on adolescent MDD was two-fold; firstly, it is the mental illness most prevalent in adolescence with accumulating evidence of altered neural activity underlying social-affective processing; secondly, the Mood-risk adolescents included in this study are at increased risk for mood disorders, particularly for MDD, by virtue of having a parent diagnosed with a mood disorder. We chose to examine implicit emotional processing of

happy faces (as opposed to using a task requiring explicit attention to the emotional content), because such tasks have been associated with robust activation of limbic and subcortical brain regions implicated in face processing in healthy individuals (Blumberg et al., 2005; Lange et al., 2003; Surguladze et al., 2003). Furthermore, alterations in prefrontal-limbic regions have consistently been shown using implicit emotion processing tasks in adult MDD populations (see Stuhrmann et al., 2011 for review). Using a similar implicit emotion processing task would thus allow us to probe this neural circuitry in adolescents with and at risk for MDD.

To the best of our knowledge, no study to date has explicitly examined functional connectivity between neural regions implicated in the processing of cues of social reward, in healthy adolescents at risk for mood disorders, and adolescents with a mood disorder. This is important because elucidating the neural underpinnings of social-affective processing in youths with and at risk for mood disorders will help advance our understanding of how alterations in neural activity and connectivity during emotional face processing, may be associated with changes in social-affective development in adolescents. Based on the limited available neuroimaging literature in adolescent MDD, and in line with findings in the adult literature, we hypothesized that: i) adolescents with MDD would show lower activation in limbic (amygdala, striatum) regions to happy faces (both 100% and 50% vs. neutral faces) and concurrent lower activation in lateral prefrontal regions, compared to healthy adolescents at risk for mood disorders and healthy adolescents at low risk. ii) in line with neurobiological models of MDD that implicate altered prefrontal-subcortical connectivity as a neural substrate for reduced cognitive control of social-affective stimuli in MDD, we also hypothesized that MDD adolescents would exhibit lower functional connectivity between lateral prefrontal and limbic regions during the processing of happy faces (both 100% and 50% vs. neutral), compared to healthy adolescents at risk for mood disorders and healthy adolescents at low risk. iii) healthy offspring at risk for mood disorders would show elevated DLPFC and VLPFC activation and increased lateral PFC-limbic connectivity during the processing of happy faces (both 100% and 50% vs. neutral faces), compared to both MDD and healthy adolescents. This hypothesis is consistent with the model proposed above and recent evidence implicating elevated lateral prefrontal cortical activity in youths at risk for mood disorders (Ladouceur et al., 2013; Lee et al., 2014).

2. METHODS

2.1 Participants

A total of 111 participants (8–17 years old) completed the study, including 29 adolescents with MDD (MDD; mean age 16.0, S.D. \pm 1.2), 39 healthy offspring at high familial risk for MDD or BD (Mood-risk; mean age 13.4, S.D. \pm 2.5) and 43 healthy offspring at low familial risk for mood disorders (HC; mean age 14.6, S.D. \pm 2.2). There was a significant difference in age between the three groups (see Table 1). We therefore included age as a covariate in all of our second-level statistical analyses. Each participant's data included here satisfied our imaging quality control criteria (see below). Depressed patients were recruited from existing studies and a clinic for depressed youth. Inclusion criteria for depressed patients included a lifetime history of MDD according to Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition (DSM-IV) criteria. All participants were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997), which is a semi-structured clinical interview, to determine the presence of current and lifetime psychiatric disorders (Kaufman et al., 1997). Healthy offspring at risk for mood disorders and HC adolescents were excluded if they endorsed any DSM-IV criteria on the KSADS-PL. On the *day of the scan*, participants were screened for current *DSM-IV* Axis I psychiatric diagnoses reported by parents, using the Stony Brook Symptom Inventory (Gadow and Sprafkin, 1998) to ascertain that they had not developed any new psychiatric disorders since the initial assessment with the K-SADS-PL. Of the 29 depressed adolescents, 16 were actively taking antidepressant medication. Mood-risk and a subset of the HC were recruited from the Bipolar Offspring Study (BIOS), an ongoing longitudinal study examining the psychopathology and functioning of offspring of individuals diagnosed with BD and offspring recruited from the community (Birmaher et al., 2009). Mood-risk adolescents were healthy but at increased risk for psychopathology, particularly for depression. They had at least one parent diagnosed with either MDD or BD (see Table 1). As stated above, HC were recruited from BIOS and via advertisements in pediatric practices. HC had no first-degree relatives with a history of recurrent unipolar depression, mania, hypomania, or psychosis, and/or second-degree relatives with a history of mania, hypomania, or psychosis. In addition to having no family history of MDD or BD, they also had no lifetime psychiatric diagnoses. Additional exclusion criteria for all participants were: Wechsler Intelligence Test score <80 (Wechsler, 1999), neurological disorders, history of head trauma, medical conditions including epilepsy, stroke, diabetes, lupus and other vascular disorders, substance abuse/dependence, pregnancy, or presence of metal in the body that would contradict an MRI. Imaging data for the depressed adolescents and a subset of the healthy offspring (Mood-risk and HC) recruited into this study have been published previously using this task, with happy and angry faces (Pan et al., 2013) and with happy and fearful faces (Mourao-Miranda et al., 2012), respectively. All participants were scanned at the Brain Imaging Research Center, Pittsburgh and underwent the same imaging protocol (see below). This study was approved by the University of Pittsburgh Institutional Review Board. To participate, children and their parents were required to sign assent and consent forms, respectively.

2.2 Self-reports

Self-report measures were also used to establish a diagnosis of depression, and to assess for depressive and anxiety symptoms in the Mood-risk and HC groups. All participants and their parents completed the parent and child self-report versions of the Screen for Childhood Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1999) respectively, and children completed the Peterson Pubertal Developmental Scale (Petersen et al., 1988), which assessed pubertal status. For the assessment of depression symptoms, Mood-risk and HC adolescents completed the Mood and Feelings Questionnaire (MFQ) and depressed adolescents completed the Beck Depression Inventory (BDI; Beck et al., 1961) (Table 1).

2.3 fMRI Paradigm

Participants underwent a 90-minute MRI scan during which they completed two runs of a 6-minute, well-validated emotional face gender labeling event-related paradigm, examining

neural activity to positively and negatively valenced facial expressions compared to neutral expressions. Given the focus of our study was on examining neural activity to cues of social reward, we present findings from the positively valenced (i.e., happy vs. neutral) run of the task only. Participants completed the task as part of a larger neuroimaging protocol that included other emotional processing and cognitive control tasks. The order in which participants received the tasks during the scan was counterbalanced across participants. The gender labeling task has been previously employed by our group in several fMRI studies of individuals with and at risk for BD and MDD and is described in detail elsewhere (Hassel et al., 2008; Ladouceur et al., 2011; Pan et al., 2013; Versace et al., 2010). Furthermore, as stated above, there was a difference in the selection of the negatively valenced task used in previous studies: fearful faces were used in the Mood-risk and HC groups, whereas angry faces were used in the MDD group. Briefly, the task comprised happy and neutral face stimuli comprising neutral (0%), mild (50%) and prototypical (100% intensity) emotion. Mild emotional intensity images (50% happy faces) were included in the paradigm, as these are thought to be more representative of the mild emotional expressions observed in everyday life. In addition, using mild emotional intensity facial expressions may be more sensitive (compared to prototypical expressions) to detecting abnormalities in neural activity supporting emotion processing, as shown in individuals with Bipolar Disorder (Hassel et al., 2008; Lawrence et al., 2004) and MDD (Pan et al., 2013). Each stimulus was presented for 2 sec. with a mean inter-stimulus interval of 4.9 sec. during which a fixation cross was displayed. Subjects viewed 20 neutral, 20 mild, and 20 prototypical faces. Subjects were asked to respond with their index finger or the middle finger to indicate whether the actor in the picture was a woman or a man and were asked to respond as quickly as possible.

2.4 fMRI Data Acquisition

Scans were acquired on a 3T Siemens Allegra MRI scanner at the Brain Imaging Research Center (BIRC), Pittsburgh. Functional T2* weighted images were acquired using a reverse gradient-echo EPI sequence (34 axial slices acquired parallel to the anterior-posterior commissure, TR/TE: 2000/25msec; pulse angle: 90°; FOV: 205 mm; acquisition matrix: 64×64; slice thickness: 3mm (no gap). High resolution T1-weighted images were acquired using a 3D MPRAGE sequence (208 sagittal slices, TR/TE: 1630/2.48ms; pulse angle: 8°; FOV: 200mm; acquisition matrix: 256×256; slice thickness: 0.8mm.

2.5 Behavioral Data

Mean percent accuracy scores and correct-trial reaction times were computed for each condition for each participant. Data were analyzed using a one-way analysis of variance (ANOVA), covarying for age, to examine the main effect of group using SPSS v. 20.

2.6 fMRI Data Analysis

2.6.1 Image Preprocessing—Preprocessing was performed with Statistical Parametric Mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, UK). Functional data for each participant were first corrected for differences in acquisition time between slices and then corrected for motion by aligning each participant's time series to the first image using least squares minimization and a six-parameter (rigid body) spatial transformation.

Participants' data were excluded if movement in the translational or rotational planes exceeded 2mm or 2°, respectively. These images were then co-registered to each participant's anatomical image, segmented and spatially normalized to the standard Montreal Neurological Institute (MNI) template, and smoothed with a Gaussian kernel of 6-mm full-width at half-maximum.

2.6.2 Individual and Group-level Analyses—For first-level analyses, model specification and estimation were performed using a General Linear Model (GLM) within SPM8. For the first-level, a fixed-effect model was defined by entering emotion condition (emotional face: happy 50% vs. fixation, happy 100% vs. fixation, neutral) as separate conditions in an event-related design matrix. Trials were modeled using the canonical hemodynamic response function. A high-pass filter of 128 seconds was used to remove low frequency drifts. Motion-related regressors were included as covariates of no interest into the GLM to control for signal change related to motion. Contrast maps from first-level analyses (i.e. 100% happy vs. fixation, 50% happy vs. fixation, neutral face vs. fixation, 100% happy vs. neutral, 50% happy vs. neutral) were entered into second-level analyses (random-effects) using a full factorial model. Our analyses focused on the happy 100% vs. neutral and happy 50% vs. neutral contrasts.

For second-level, between-group analyses, a whole-brain random-effects 3×2 [Group (MDD, Mood-risk, HC)] \times [Emotional face (100% happy vs. neutral, 50% happy vs. neutral)] factorial design was used in SPM8. Age was included as a covariate in the 2nd level model in order to control for potential effects of brain development on brain activity and connectivity (as in Ladouceur et al., 2013; Pan et al., 2011; Pan et al., 2013). We used a whole-brain approach as no prior studies have directly compared brain activation and functional connectivity in adolescents with MDD, adolescents at risk for a mood disorder, and HC, with a specific focus on happy faces. As such, we did not have a priori hypotheses about specific regions, and rather, formulated our hypotheses based on broader lateral PFC- limbic networks that are implicated in social-affective processing (in particular emotional face processing), and that are implicated in youth BD and MDD. This allowed us to look at a group \times condition interaction on brain activity to happy (100% and 50% vs. neutral) faces. For this analysis, results were thresholded at $p < .005$ with a family-wise error (FWE) ($p < .05$) cluster-wise correction determined using AlphaSim (Ward, 2000) with MonteCarlo simulations (1000 simulations with cluster forming threshold of $p < .05$). Using a whole brain approach with AlphaSim cluster-wise correction to determine significant whole brain clusters, has been used by our group previously (Hassel et al., 2008; Ladouceur et al., 2011). Then, to unpack any significant interactions, and to examine between-group differences, post-hoc whole-brain t-tests, Bonferroni corrected, were ran in SPM on the happy 100% (vs. neutral) and happy 50% (vs. neutral) contrasts. This yielded a threshold of $p < .05/6 = .008$ for the 6 independent t-tests used to compare groups on each of the contrasts.

2.6.3 Functional Connectivity Analyses—We used generalized psychophysiological interaction (gPPI) analyses (gPPI; <http://www.nitrc.org/projects/gppi>) (McLaren et al., 2012) in SPM8 to examine functional connectivity associated with the processing of happy (100% and 50% vs. neutral) faces. For this analysis the right ventral putamen and right DLPFC

were chosen as seed regions. The right ventral putamen was chosen as it showed a significant group x condition interaction. The right DLPFC was chosen because it showed strong between group differences for 100% intensity happy faces (see Results section). gPPI is a valuable method for examining how brain regions are functionally connected in a task-dependent manner (McLaren et al., 2012). Specifically, gPPI analyses reflect changes in a regression slope associated with the differential blood oxygenation level dependent (BOLD) response from one neural region (i.e. physiological response) under the influence of experimental contexts (i.e. psychological condition) (Friston et al., 1997). At the first-level, the psychophysiological (PPI) variable was computed for each participant by forming an interaction term between the vectors of each task condition (i.e., happy vs. fixation, neutral vs. fixation, happy 100% vs. neutral, happy 50% vs. neutral) and the extracted, deconvolved BOLD signal from the right ventral putamen and right DLPFC. The right ventral putamen seed was defined as a 3mm sphere, centered at the peak voxel ($x=21, y=3, z=-5$) of the ventral putamen cluster from the primary analysis. The right DLPFC seed was defined as a 5mm sphere centered at the peak voxel ($x=45, y=36, z=30$) of the DLPFC cluster from the post-hoc t-tests for the 100% happy vs. neutral contrast. Interaction terms were then entered into a new GLM with the original eigenvariate time-series, task onset vectors and six movement parameters which were regressors of no interest. The resultant contrasts for the happy 100% vs. neutral and happy 50% vs. neutral PPI for each participant were positively weighted, given that our analysis focused on group differences in ventral putamen and DLPFC functional connectivity. The contrasts from the PPI analysis were submitted to second-level random-effects analyses in SPM8. As done in our analysis above, whole brain functional connectivity results were analyzed with a 3×2 ANOVA model thresholded at $p < .005$ with a FWE ($p < .05$) cluster-wise correction using AlphaSim. Separate ANOVA models were used for the ventral putamen and DLPFC seed regions. Similarly, between-group differences in functional connectivity were examined with post-hoc whole-brain t-tests, Bonferroni corrected. As stated above, this yielded a threshold of $p < .05/6 = .008$ for the 6 independent t-tests used to compare groups on each of the contrasts.

2.7 Secondary analyses

We conducted secondary analyses to examine a) if reduced ventral putamen and elevated DLPFC activation to 50% and 100% intensity happy faces respectively, in the Mood-risk group was being driven by the specific type of familial risk (i.e., MDD or BD); b) the relationship between indices of DLPFC functional connectivity and depression and anxiety symptoms in MDD adolescents; and c) the extent to which antidepressant medication in the MDD group affected our functional neuroimaging results. Please see Supplementary material for these analyses.

3.1 RESULTS

3.1 Behavioral data

Accuracy—There was no significant main effect of group or group x emotional face condition interactions ($p < .1$). **Reaction Times**: There was no significant main effect of group or group x emotional face condition interactions ($p > .1$). Please see Supplementary Table S1.

3.2 fMRI Results

In the following section we present the fMRI and gPPI results examining neural activation and functional connectivity during the processing of cues of social reward. We used AlphaSim, which served as a FWE correction ($p < .05$) using a spatial extent threshold. For functional activation the minimum estimated cluster sizes for significant whole brain clusters were: group x condition interaction = 57 voxels; main effect of group = 58 voxels; main effect of condition = 60 voxels. For functional connectivity with the ventral putamen, the minimum estimated cluster sizes were: group x condition = 66 voxels; main effect group = 65 voxels; main effect condition = 58 voxels. For functional connectivity with the DLPFC the minimum estimated cluster sizes were: group x condition interaction = 58 voxels; main effect group = 66 voxels; main effect condition = 61 voxels.

3.3 Functional activation results

A 3×2 ANOVA for happy faces (100% and 50% vs. neutral), covarying for age, revealed a significant group x condition interaction in the right ventral putamen (peak coordinates $x=21, y=3, z=-5$; $F(2,215)=5.43, p < .005$ corrected, $K_e=59$ voxels). There was no main effect of group ($p > .005$) but a main effect of condition in the right VLPFC (peak coordinates $x=33, y=54, z=-6$; $F(2,215)=10.43, p < .005$ corrected, $K_e=107$ voxels). Post-hoc t-tests showed that the group x condition interaction was being driven by the Mood-risk adolescents who showed lower activation in the right ventral putamen compared to HC adolescents when viewing 50% intensity happy faces ($p < .008$, Bonferroni corrected) (Figure 1a). There were no significant between group differences in putamen activation when viewing 100% intensity happy faces (all $p > .008$). Post-hoc t-tests for the happy 100% vs. neutral contrast revealed that Mood-risk adolescents showed increased activation in the right DLPFC/BA 9 compared to HC adolescents, when viewing 100% intensity happy faces (peak coordinates $x=45, y=36, z=30$; $p < .008$, Bonferroni corrected) (Figure 1b). There were no significant differences in DLPFC activation to 100% intensity happy faces between the Mood-risk adolescents and MDD adolescents ($p > .008$) or between MDD adolescents and HC ($p > .008$).

3.4 Functional connectivity results

Ventral putamen—A 3×2 ANOVA for happy faces (100% and 50% vs. neutral), covarying for age, revealed no significant group x condition interaction ($p > .005$). There were also no significant main effects of group or condition ($p > .005$).

DLPFC—A 3×2 ANOVA for happy faces (100% and 50% vs. neutral), covarying for age, revealed a significant main effect of group in the right VLPFC (peak coordinates $x=42, y=39, z=0$; $F(2, 215)=12.72, p < .005$ corrected, $K_e=205$ voxels). There was no significant group x condition interaction or main effect of condition ($p > .005$). Post-hoc t-tests showed that MDD adolescents had lower positive functional connectivity between the right DLPFC and right VLPFC compared to HC adolescents when viewing 50% and 100% intensity happy faces (both $p < .008$) (Figure 2). There were no significant differences in DLPFC – VLPFC functional connectivity to 50% or 100% intensity happy faces between the Mood-

risk adolescents and MDD adolescents ($p>.008$) or between Mood-risk adolescents and HC ($p>.008$).

4. DISCUSSION

The specific aim of this study was to examine alterations in lateral PFC-limbic circuitry during the processing of cues of social reward in adolescents with MDD, and the extent to which such alterations are present in adolescents at risk for mood disorders, by virtue of having a parent diagnosed with either MDD or BD. In partial support of our hypotheses, we found alterations in lateral PFC and subcortical activation in the Mood-risk group to mild and intense happy faces. Specifically, Mood-risk adolescents compared to HC adolescents showed lower right-sided ventral putamen activation to 50% intensity happy faces but elevated right-sided DLPFC activation to 100% intensity happy faces. Functional connectivity of the right ventral putamen however, was not altered in the Mood-risk or MDD groups. In contrast, functional connectivity of the DLPFC was altered in the MDD group, with depressed adolescents showing lower functional connectivity of the right DLPFC with the VLPFC to 100% and 50% intensity happy faces. Collectively our results suggest that elevated activity in the DLPFC and concomitant lower activity in the ventral putamen to cues of social reward in healthy adolescents at-risk for mood disorders may be associated with risk or resiliency, given that Mood-risk adolescents were healthy at the time of the scan. Alterations in connectivity of the DLPFC however, are only apparent as youth develop depression.

Our finding of elevated DLPFC activation to 100% intensity happy faces in Mood-risk adolescents compared to HC is consistent with recent findings in youth at high familial risk for BD during the performance of an emotional working memory task with emotional face distracters (Ladouceur et al., 2013). The findings are also consistent with a recent meta-analysis in pediatric BD showing that ‘high-risk’ youth, defined as having a biological parent diagnosed with BD, show elevated DLPFC activation during tasks that require attentional control of emotional stimuli, and cognitive flexibility (Lee et al., 2014).

Emotional faces are salient stimuli that capture attention rapidly and compete for cognitive resources (Dolcos and McCarthy, 2006). Happy faces in particular, are thought to be particularly salient in adolescence, signaling potential social reward (Ernst et al., 2006; Steinberg, 2008). A recent study by Cromheeke and Mueller (2015) showed that happy faces impaired working memory performance in adolescents when attention was being paid to a non-affective feature of the face, and that this interfering effect was not observable in adults. In neuroimaging studies using similar cognitive tasks with emotional distracters, greater activation of the lateral PFC in response to emotional distracters has been associated with greater modulation of attention in order to resist interference (Anticevic et al., 2010; Dolcos et al., 2006). Our finding of elevated DLPFC activation in the Mood-risk group was however, only observed for 100% intensity happy faces. Elevated DLPFC activation to intense emotional faces may indicate a preferential allocation of attention to faces displaying higher intensities of emotion, compared to more mild expressions of happiness observed in everyday life. A greater mobilization of attention to intense happy faces could potentially facilitate increased social-affective processing to cues of social reward. Behaviorally, this

may manifest in increased reward-seeking behavior and greater reactivity to approach-related stimuli in at-risk adolescents.

We found lower activation in the ventral putamen to 50% intensity happy faces in Mood-risk adolescents. The directionality of this effect however, was not consistent with our hypothesis. We also didn't find any differences in subcortical activation to 50% or 100% intensity happy faces in MDD adolescents. There is increasing evidence for elevated right-sided lateral PFC activity and increased connectivity of the lateral PFC with limbic (amygdala) regions to happy faces in youth at risk for BD (Ladouceur et al., 2013; Manelis et al., 2015; Olsavsky et al., 2012; Thomas et al., 2014), which may reflect increased reward sensitivity. Findings in youth at risk for MDD have generally shown the opposite; that is, reduced ventral striatal activity to monetary reward as well as social cues of reward (happy faces) (Gotlib et al., 2010; Monk et al., 2008; Sharp et al., 2014). The finding of reduced ventral putamen activity in Mood-risk adolescents in the present study was observed for 50% intensity happy faces only. This could reflect reduced reactivity to mild happy faces, perhaps because they are perceived as less salient and therefore less socially rewarding, in adolescents at risk of mood disorders. Activity of the ventral putamen to prototypical happy faces (100% intensity) in contrast, was comparable to HC, suggesting that regions implicated in reward processing and salience detection including the ventral putamen, require a higher degree of intensity to become activated in adolescents at risk for mood disorders. This is supported by behavioral studies that show that youth at risk for BD need more intense emotional expressions to correctly identify emotions (Brotman et al., 2008). There was also a trend for lower ventral putamen activity to 50% intensity faces in MDD adolescents, however this didn't reach statistical significance. Some studies in adolescents with and at risk for MDD have reported diminished ventral striatal activity (Monk et al 2008) and elevated amygdala activity (Henje Blom et al., 2015; Yang et al., 2010) to happy faces (although evidence for amygdala hyperactivity in adolescent MDD has been more consistent for studies examining negative emotional processing (see Kerestes et al., 2013 for review).

When comparing our results to previous studies it is important to note however, differences in experimental paradigms that have been used (e.g., implicit vs. explicit emotion face processing) and the type of face stimuli that have been employed (e.g., static faces vs. dynamic faces). Using dynamic faces for example, that systematically vary in face emotion intensity levels, may help prevent amygdala habituation (Breiter et al., 1996) and therefore be more sensitive to detecting subtle alterations in amygdala activation. It is also important to consider the variability in age ranges used to define "adolescence" across studies, and the extent to which studies accounted for the possible effects of age. Whilst some fMRI studies in youths with and at-risk for mood disorders have recruited participants using narrow age ranges (e.g., 13–17 years old; Yang et al., 2010), others have used wider age ranges encompassing 7–17 year olds (Ladouceur et al., 2013; Manelis et al., 2015; Stoddard et al., 2015) and 10–18 year olds (Monk et al., 2008). In addition, not all studies have covaried for age in their analyses (Stoddard et al., 2015; Yang et al., 2010), which is important given evidence of age-related changes in neural circuitry involved in emotion processing (e.g., amygdala) and the attentional control of emotion (e.g., DLPFC) (Olesen et al., 2007; Yurgelun-Todd and Killgore, 2006).

Taken together, our finding of elevated DLPFC activation to intense happy faces together with lower subcortical activation to mild intensity happy faces in Mood-risk adolescents suggests that altered lateral PFC and ventral putamen activation could be associated with risk for affective disorders in early adolescence. Specifically, lower ventral putamen activation to mild expressions of happiness that are representative of the mild emotional expressions observed in everyday life, may reflect reduced reactivity to rewarding stimuli in Mood-risk adolescents. At higher intensities of happiness, in the absence of any subcortical activation differences, DLPFC activation was elevated in Mood-risk adolescents, possibly reflecting increased mobilization of attention to cues of social reward. This could facilitate increased reward-seeking behavior that, if not regulated appropriately, could be associated with altered social behavior leading to peer rejection and social isolation. Alternatively, elevated DLPFC activation to 100% intensity happy faces may be a neurobiological alteration that is associated with resilience, reflecting compensatory activation to enable the Mood-risk adolescents to achieve equal performance on the task.

Adolescents with MDD showed lower functional connectivity of the right DLPFC with the VLPFC to both 100% and 50% intensity happy faces compared to HC. Lateral prefrontal regions including the DLPFC together with the VLPFC, are implicated in higher-order cognitive control processes and are typically engaged by tasks that require integration of information to support sustained cognitive performance and attentional control (Dosenbach et al., 2007; Vincent et al., 2008). The gender-labeling task used in the present study assesses implicit processing of cues of social reward, and requires minimal engagement of cognitive resources. Greater lateral PFC engagement across groups to happy faces (and differences between groups) would perhaps be expected if the task required an explicit, overt response to the emotional content of the face or cognitive control in order to resist interference of emotional distracters, as has previously been shown in youths at risk of BD (Brotman et al., 2014; Ladouceur et al., 2013). However, given the saliency of emotional faces and increased sensitivity to cues of social reward in adolescence, the emotional expression of the faces in this task may have required greater attentional control to resist interference. Lower connectivity between the DLPFC and VLPFC during the processing of happy faces in adolescent MDD compared to HC could therefore be considered as disrupted cognitive control of emotion, consistent with neurobiological models of adult mood disorders (Mayberg, 1997; Phillips et al., 2008; Price and Drevets, 2012). We note that although this finding of lower connectivity with the VLPFC was only significantly different from controls, there was a trend for lower connectivity with the VLPFC particularly for 100% intensity happy faces in Mood-risk adolescents compared to HC (Figure 2). Together with our finding of elevated DLPFC activation in Mood-risk adolescents, we can speculate that alterations in functional connectivity of lateral PFC regions may be subtle and more localized in individuals at-risk for mood disorders. As illness progresses, however, alterations in DLPFC functional connectivity become more pronounced and wide-spread. Longitudinal studies that examine, from a dimensional perspective, how alterations in functional connectivity to cues of social reward become apparent as youths at-risk for MDD develop depressive symptoms, will be able to directly answer this research question. Such studies could thus determine the extent to which such alterations in functional connectivity could represent neural underpinnings of risk for depression in vulnerable adolescents.

There are limitations of the present study. Firstly, there were significant differences in age and pubertal maturation between the MDD, Mood-risk and HC groups. Given the strong correlation between age and pubertal maturation processes, MDD adolescents were at a more advanced pubertal maturation stage compared to the Mood-risk and HC groups. We did however, account for age differences using a continuous approach through analysis of covariance in our statistical model. In addition, it was necessary to recruit depressed adolescents who were actively taking antidepressant medication. Although secondary analyses showed that antidepressant medication did not impact our results, future studies that recruit larger samples of depressed adolescents will be able to examine the specific effects of antidepressant medication on brain activity. Furthermore, due to slight differences in protocols, we were not able to have a comparable IQ measure for all participants. This reduced our ability to effectively compare the groups and is a limitation of the study. Finally, the focus of our study was to examine neural function in adolescents at risk for affective disorders in general, and not risk for BD or MDD specifically. Furthermore, our results of reduced ventral putamen activation to 50% intensity and elevated DLPFC activation to 100% intensity happy faces in Mood-risk adolescents were not explained by type of familial risk (see Supplementary material for post-hoc t-tests comparing adolescents at risk for BD vs. MDD). However, the smaller sample of adolescents at risk for MDD compared to those at risk for BD in the current study is a limitation and may have limited our ability to detect statistically significant differences in neural function specific to type of familial risk. Future studies should attempt to recruit equal sample sizes of healthy adolescents at risk for MDD and BD. In addition, it would have been ideal to have a group of BD youth in the study. This would have allowed us to compare youth with and at risk for both MDD and BD, and ascertain disease-specific neural mechanisms; that is, potential neural alterations that may distinguish between risk for BD vs. MDD.

In conclusion, this is the first study to examine functional connectivity between neural regions implicated in the processing of cues of social reward, in adolescents with MDD and healthy adolescents at risk for MDD and BD. Our findings of altered ventral putamen and DLPFC activation in the absence of corresponding functional connectivity changes with these regions in offspring at risk for mood disorders, together with lower DLPFC functional connectivity in MDD adolescents to 100% and 50% intensity happy faces suggests that lowered ventral putamen activation and elevated DLPFC activity may be associated with risk or resilience for mood disorders. Alterations in DLPFC however, are specific to depressed mood state, becoming apparent only as illness develops. Future longitudinal follow-up studies will help determine whether such alterations in neural activity to cues of social reward confer risk or resiliency in healthy offspring that have a parent with a mood disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examine functional connectivity in adolescents with and at risk for mood disorders
- At-risk adolescents showed elevated DLPFC and lowered ventral putamen activation to cues of social reward
- Adolescents with MDD showed reduced DLPFC functional connectivity with the VLPFC
- Elevated DLPFC and lowered ventral striatal activation in at-risk adolescents may be a marker of risk or resiliency
- Altered DLPFC functional connectivity may be a marker of depressed mood state

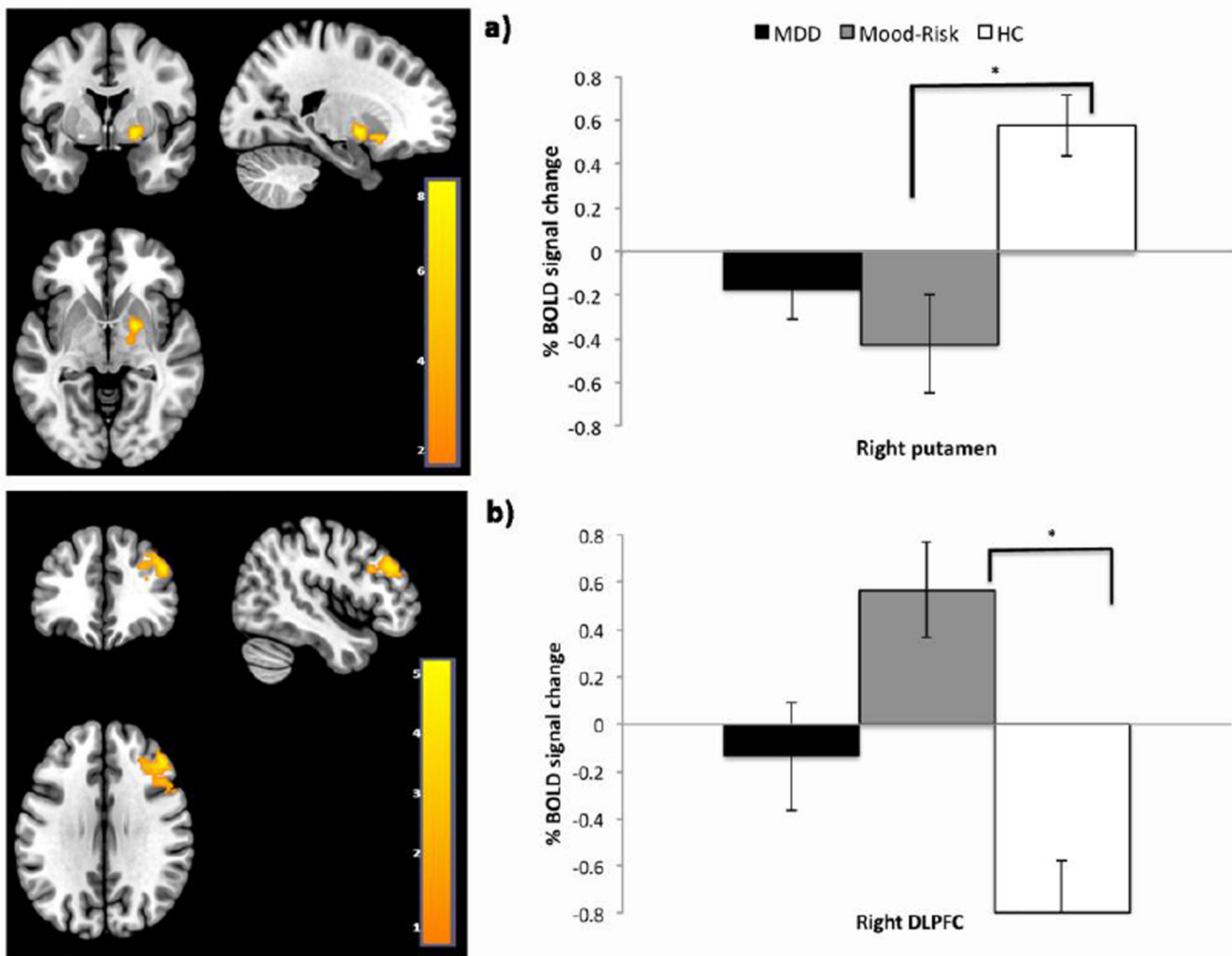


Figure 1.
a) LEFT: Whole-brain 3 × 2 analysis of variance displaying a group x condition interaction in the right ventral putamen to 50% intensity happy (vs. neutral) faces. **RIGHT:** Eigenvariates representing estimates of mean changes in BOLD signal activation of the ventral putamen that was significantly lower in Mood-risk adolescents compared to HC ($p < .008$, Bonferroni corrected). **b) LEFT:** Whole-brain 3 × 2 analysis of variance displaying a main effect of group in the right DLPFC to 100% intensity happy (vs. neutral) faces. **RIGHT:** Eigenvariates representing estimates of mean change in BOLD signal activation of the DLPFC that was significantly greater in Mood-risk offspring compared to HC adolescents ($p < .008$, Bonferroni corrected).

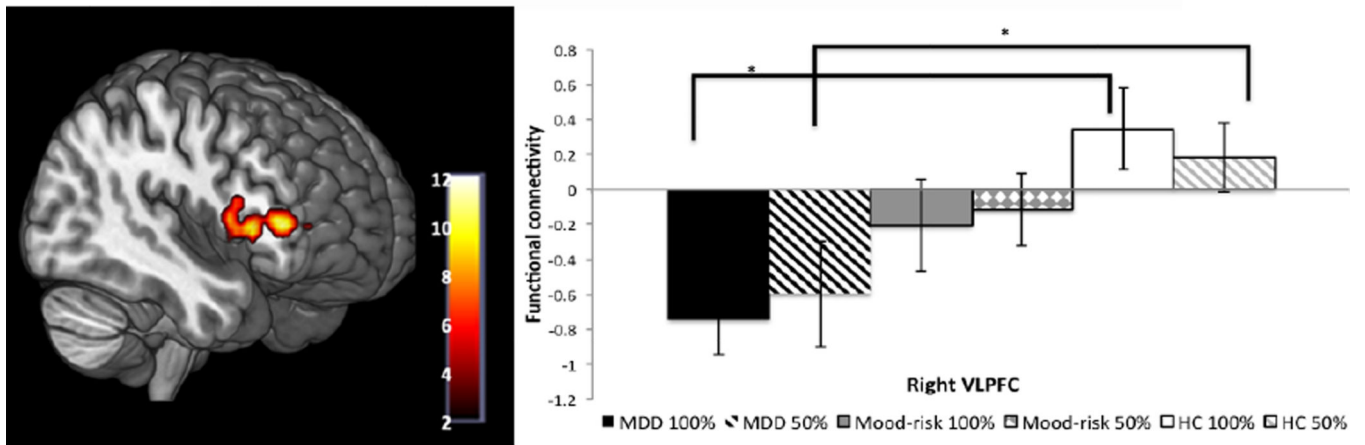


Figure 2. Significant between-group differences in functional connectivity of the right DLPFC. LEFT: Rendered sagittal view displaying the region of the right ventrolateral prefrontal cortex ($x=42$, $y=39$, $z=0$) that showed significantly lower functional connectivity with the DLPFC in MDD adolescents to 50% and 100% intensity happy faces compared to HC adolescents ($p < .008$, Bonferroni corrected). RIGHT: Eigenvariates representing estimates of mean DLPFC-VLPFC functional connectivity for 50% and 100% intensity happy faces.

Table 1
Demographic and clinical characteristics of adolescents with Major Depressive Disorder (MDD), healthy offspring at risk for mood disorders (Mood-risk) and healthy controls (HC)

	MDD n=29	Mood-risk n=39	HC n=43	Statistics	p value (two-tailed)	group difference
Age (years), (S.D.)	16.0 (1.23)	13.4 (2.52)	14.6 (2.25)	$F(2,108)=12.26$	<0.001	MDD>Mood-risk MDD>HC
Female, % (n)	62 (18)	53 (21)	65 (28)	$\chi^2(2)=1.1$	0.56	
Pubertal Development Scale, mean (S.D.)	3.58 (0.50)	2.38 (0.78)	2.83 (0.75)	$F(2,108)=24.0$	<0.001	MDD>Mood-risk MDD>HC
SCARED-child, mean (S.D.)	16.6 (13.51)	12.5 (9.84)	8.9 (6.75)	$F(2,108)=5.28$	0.006	MDD>Mood-risk MDD>HC
SCARED-parent, mean (S.D.)	18.34 (11.63)	8.33 (7.82)	4.67 (5.79)	$F(2,108)=23.83$	<0.001	MDD>Mood-risk MDD>HC
BDI, mean (S.D.)	9.7(2.52)	-	-	-	-	-
Antidepressant treatment, % (n)	55(16)	-	-	-	-	-
Psychiatric diagnoses (yes/no)	yes	no	no	-	-	-
Parent diagnosis (BD-I or II/MDD)*	-	27/11	-	-	-	-

Abbreviations: MDD, Major Depressive Disorder; HC, healthy controls; SCARED, Screen for Childhood Anxiety related Disorders; BDI, Beck Depression Inventory; BD-I, Bipolar Disorder type I; BD-II, Bipolar Disorder type II

* Information inconclusive for one participant