Journal of Affective Disorders 192 (2016) 143–152

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Altered neural function to happy faces in adolescents with and at risk for depression

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ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form
24 November 2015
Accepted 11 December 2015
Available online 21 December 2015

Keywords:
Adolescence
Major depressive disorder
Social-affective processing
Functional connectivity

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, S.D. 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, S.D. 2.5 years) and 43 healthy control adolescents, having parents with no psychiatric disorder (HC; M age 14.6, S.D. 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.
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.

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

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http://dx.doi.org/10.1016/j.jad.2015.12.013
0165-0327/

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 et al. (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 et al. (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 BD 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 BD 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 (vs. neutral) faces 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