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Research paper

Anomalous prefrontal-limbic activation and connectivity in youth at high-risk for bipolar disorder☆

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ABSTRACT

Objective: Abnormal prefrontal-limbic brain activation in response to facial expressions has been reported in pediatric bipolar disorder (BD). However, it is less clear whether these abnormalities exist prior to onset of mania, thus representing a biomarker predicting development of BD.

Methods: We examined brain activation in 50 youth at high risk for BD (HR-BD), compared with 29 age- and gender-matched healthy control (HC) subjects. HR-BD was defined as having a parent with BD, as well as current mood or attentiondeficit/ hyperactivity disorder (ADHD) symptoms, or a history of at least one depressive episode. FMRI data were collected during an implicit emotion perception task using facial expression stimuli. Activation to fearful faces versus calm faces was compared between HR-BD and HC groups, including analyses of functional connectivity, and comparison of allele subgroups of the serotonin transporter (5-HTTLPR) gene.

Results: While viewing fearful versus calm faces, HR-BD youth had significantly greater activation than HC youth in the right amygdala, ventrolateral prefrontal cortex (VLPFC), superior frontal cortex, cerebellum, and lingual gyrus. HR-BD youth, relative to HC youth, had greater functional connectivity between the right amygdala and the VLPFC as well as visual cortical regions Within the HR-BD group, youth with the *s*-allele had a trend for greater activation in the right amygdala and subgenual cingulate cortex

Conclusions: Similar to youth with BD, youth at high risk for BD have greater activation than healthy controls in the amygdala and ventrolateral prefrontal cortex in response to fearful faces, as well greater functional connectivity between these regions. HR-BD youth with the s-allele of the 5-HTTLPR gene may be at greatest risk for developing BD.

1. Introduction

Bipolar disorder (BD) is a chronic disorder having high morbidity and mortality, and leading to health care costs of 45 billion dollars per year (Kleinman et al., 2003). Up to 2–3% of the world population may be affected by bipolar spectrum disorders (Merikangas et al., 2011). Therefore, it is important to identify risk factors that will inform our understanding of the developmental pathophysiology of BD, suggest early biomarkers, and ultimately help ameliorate the course of BD or prevent the onset of mania altogether (Chang et al., 2006). Retrospective studies clearly indicate that BD begins in childhood or adolescence for 50–66% of cases (Drevets et al., 2008; Leverich et al., 2007; Perlis et al., 2004), either with sub-threshold symptoms or a full manic or depressive episode. Yet, a DSM diagnosis can only be made from observation, and only after the full illness has developed. Identifying objective biological risk factors for BD could lead to reliable early identification and prevention, and shed light on the mechanisms of BD development.

Compared to the general population, offspring of parents with BD are at increased risk for psychopathology, and particularly for mood disorders (Axelson et al., 2011; Chang et al., 2003). Such offspring who are experiencing symptoms of depression and/or ADHD, referred to here as HR-BD, are at particularly high risk, and thus they are an ideal cohort for examining risk factors predating mania.

FMRI findings in youth with BD indicate either over- or under-activation of prefrontal emotion regulatory regions, including

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dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and anterior cingulate cortex (Roybal et al., 2012). Limbic hyperactivation, particularly in the amygdala, also has been reported in studies of mixed-mood and euthymic patients (Garrett et al., 2012; Pavuluri et al., 2007; Rich et al., 2006). However, it is not clear if these functional abnormalities are present before the onset of mania.

Another factor that may contribute to amygdala overactivation is the short (*s*) allele polymorphism of the 5-HTTLPR region of the serotonin transporter gene. Carriers of the *s*-allele have been found to have higher amygdalar activation than those without (Hariri et al., 2002). While this association has been shown for healthy adults, such a role of the *s*-allele has not yet been shown for patients with BD or youth at high-risk for BD.

While performing facial expression perception and cognitive flexibility tasks, relatively asymptomatic bipolar offspring have greater amygdala, VLPFC, inferior parietal, and caudate activation compared with healthy controls (Kim et al., 2012; Olsavsky et al., 2012). Healthy bipolar offspring have also been found to have increased VLPFC activation in response to reward and increased amygdalar activation in anticipation of loss (Singh et al., 2014b) and altered functional connectivity in prefrontal-striatal circuits (Singh et al., 2014a). The first fMRI study of youth at high-risk for BD with symptoms of mood dysregulation was a treatment study using divalproex monotherapy (Chang et al., 2009). In this study, bipolar offspring had decreased DLPFC activation in response to emotional stimuli as depression symptom severity improved. However, without a healthy comparison group it was unknown if DLPFC activation was greater than normal at baseline. Recent studies of symptomatic bipolar offspring have demonstrated that instead, such youth appear to have relatively increased DLPFC activation (Lee et al., 2014), as well as increased amygdalar activation to emotional probes, and altered functional connectivity between amygdala and prefrontal areas (Manelis et al., 2016, 2015). These latter studies included both bipolar offspring with and without psychopathology, but findings did not change when considering either group alone.

In this study, we examined brain activation in youth at high-risk for BD, all considered symptomatic and at high-risk, using fMRI during a standard emotional faces paradigm, to determine if, similar to youth with BD, prefrontal and limbic areas would demonstrate hyperactivation compared with healthy controls. We chose to study youth already with psychopathology as they would be considered at even higher risk than those offspring without any psychopathology, who could be argued to actually be demonstrating characteristics of resilience.

We hypothesized that we would find abnormal activation in the VLPFC, DLPFC, subgenual ACC, and amygdala, and abnormal functional connectivity between these regions. Furthermore, we hypothesized that these regions would demonstrate hyperactivation preferentially for carriers of the 5-HTTLPR *s*-allele.

2. Methods

2.1. Subject recruitment and assessment

The study was approved by the Institutional Review Board, Medical Human Subjects Panel, at Stanford University. Written and oral informed consent and assent were obtained from at least one parent, and the youth, respectively.

Participating families were recruited from the Stanford Adult and Pediatric Bipolar Disorders Clinics and from the surrounding community. Inclusion criteria for HR-BD were age 9 – 18 years, a diagnosis of either major depressive disorder (MDD), BD-NOS, or attention-deficit/hyperactivity disorder (ADHD), and a biological parent with bipolar I or II disorder. We assessed current manic symptom severity using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and depression symptom severity using the Children's Depression Rating Scale – Revised (CDRS-R) (Poznanski and Mokros, 1995). Subjects with ADHD were required to have at least moderate mood symptoms, quantified by a YMRS score greater than 12 and/or a CDRS score greater than 36. Exclusion criteria were history of mania or hypomania, presence of a pervasive development disorder, a neurological condition, substance use disorder, IQ less than 80, presence of metallic implants or braces, or current hospitalization. Stimulants were discontinued for at least 24 h prior to scanning; other medications were continued. IQ was assessed by the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological-Corporation, 1999).

Parental diagnosis of BD I or II was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995). When available, the other biological parent was also assessed in this manner. Family history was obtained using the Family History – Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). Youth were assessed by the affective module of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 2001, 1996) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime (K-SADS-PL) (Kaufman et al., 1997). All subjects were evaluated either by a child psychiatrist (KC) or trained masters-level research assistant (MH), who were both aware of parental diagnosis. Current and lifetime DSM-IV diagnoses were ultimately determined by a board certified child psychiatrist (KC). based on personal interview, discussion with the research assistant, and written notes of responses to individual questions.

Healthy controls (HC) were similarly interviewed, and determined to have no DSM-IV diagnoses, were not taking psychotropic medications, had both parents without any psychiatric diagnosis (determined by the SCID), and did not have a first- or second-degree relative with BD as determined by the FH-RDC.

2.2. MRI Acquisition

Subjects were scanned on a 3 T GE Signa scanner using a custom-built head coil. Functional MRI data were collected with thirty axial slices (4 mm thick, .5 mm skip), covering the entire brain (FOV = 20 cm, 64 × 64 matrix, inplane spatial resolution = 3.43 mm). A spiral in-out pulse sequence (Glover and Law, 2001) used the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 80° and one interleave. An individually calculated high-order shim was used to reduce B0 heterogeneity.

2.3. Facial Expressions Task

Photographs of young adults with fearful, calm, and neutral facial expressions, as well as scrambled images, were presented in a block design. All faces were taken from the McArthur facial expressions set ('NimStim'; http://www.macbrain.org/resources.htm). Each block contained 8 faces of the same expression, and each face was presented for 3-seconds. Blocks of each expression were alternated throughout the task, and overall, 3 blocks of each facial expression were shown. Within each block, the presentation of male versus female faces was presented pseudo-randomly, and no faces were repeated. Subjects used a button box to push button 1 for female faces, button 2 for male faces, and alternating buttons 1 and 2 during the scrambled pictures blocks. The entire task lasted 8 min and 8 s. The task was presented using ePrime software (www.pstnet.com), which also collected responses. Subjects viewed the faces by looking directly up to see the image projected from the foot of the scanner.

2.4. FMRI data processing

Functional data were processed using SPM8 (Welcome Department of Imaging Neuroscience, London, UK). Images were reconstructed, spatially realigned to the third image, motion corrected, normalized to MNI space using a study-specific anatomical template, and smoothed