Intrinsic Amygdala Functional Connectivity in Youth With Bipolar I Disorder

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Objective: Bipolar disorder (BD) commonly begins during adolescence and may continue into adulthood. Studies in adults with BD suggest that disruptions in amygdalar neural circuitry explain the pathophysiology underlying the disorder. Importantly, however, amygdala subregion networks have not yet been examined in youth close to mania onset. The goal of this study was to compare resting state functional connectivity patterns in amygdala subregions in youth with bipolar I disorder with patterns in healthy controls.

Method: Centromedial, laterobasal, and superficial amygdala subdivisions were assessed during rest and examined in relation to clinical measures of mania in youth (14–20 years old) with bipolar I disorder who experienced only a single episode of mania (BD; n = 20) and age-matched healthy comparison youth without any personal or family history of *DSM-IV* Axis I disorders (HC; n = 23).

Results: Relative to HC youth, youth with BD exhibited decreased connectivity between the laterobasal subdivision of the amygdala and the hippocampus and precentral gyrus, and increased connectivity between the laterobasal subdivision and the precuneus. Connectivity between the right laterobasal amygdala and right hippocampus was positively correlated with levels of anxiety in BD but not in HC youth, and connectivity between the right laterobasal amygdala and right precuneus was negatively correlated with insight about bipolar illness.

Conclusion: Youth with BD have abnormal amygdala resting state network connections to regions that are critical for emotional processing and self-awareness. Longitudinal studies are needed to determine whether these aberrant patterns in youth with BD can be altered with intervention and can influence the course of disorder.

Key Words: bipolar, resting state functional connectivity, amygdala, precuneus, hippocampus

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Bipolar disorder (BD) is a complex psychiatric disorder characterized by disturbances in cognitive functions that are subserved by distributed neural networks.[1-3] Childhood onset of BD is common and is associated with a more severe course and prognosis than is onset occurring during adulthood[4,5]; thus, efforts to identify neurobiological factors associated with early onset and progression of BD are particularly important. Several lines of evidence indicate that BD is associated with impairments in key cognitive processes critical for emotional processing,[3,6,7] and with anomalies in both neural structure and function, particularly in the amygdala, hippocampus, ventrolateral prefrontal cortex (VLPFC), and dorsolateral prefrontal cortex (DLPFC), striatum, and portions of the anterior cingulate cortex (ACC).[8] These findings raise the possibility that BD arises from a disruption of connections between specific prefrontal–limbic networks. In particular, investigators have documented that, compared to adult-onset BD, childhood-onset BD is uniquely characterized by reductions in amygdala volume[9,10] and amygdala hyperactivity,[11-14] which may represent neural markers of illness onset. The intrinsic connectivity of the amygdala, however, has not been examined in youth with BD close to the onset of manic illness and may be critical to clarifying a network-based neurodevelopmental model of BD.[15]

Recent studies have used resting-state functional magnetic resonance imaging (fMRI) to characterize networks associated with BD. This procedure circumvents task-related confounds such as performance variance and probes ongoing spontaneous brain activity that provides a rich potential source of disorder-related signal change.[16] Adults with BD have been found to exhibit decreased resting-state connectivity between the pregenual ACC and amygdala, thalamus, and pallidostriatum,[17] and loss of inverse connectivity between the VLPFC and amygdala.[18] Thus, disrupted functional connectivity in key limbic and prefrontal regions may underlie the core deficits in emotional processing associated with BD.

Several studies have now used a variety of regionally specific and model-free analytic approaches to compare resting state functional connectivity between youth with BD and healthy controls. Two studies used a region of interest (ROI) analysis approach: 1 study reported increased connectivity between the left DLPFC and superior temporal cortex in youth with BD relative to healthy youth,[19] and the other reported decreased amygdala–posterior insula connectivity in BD youth.[20] Using a model-free independent components analysis approach, Wu *et al.*[21] found that youth with BD exhibited altered affective, executive, and sensorimotor networks, and that greater connectivity of the right amygdala within the affective network was associated with

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better executive function in children with BD but not in controls. Collectively, the results of these studies suggest that pediatric BD is characterized by aberrant patterns of prefrontal and limbic connectivity.

It is difficult to draw strong conclusions and to develop a clear pathophysiological model of pediatric BD from these studies, however, because they used analytic approaches that are not easily compared (e.g., regionally specific versus model free). These investigations were also limited because they combined heterogeneous samples of children and adolescents with BD without consideration of the contributions of puberty or mood state to neural findings.[22] These limitations highlight methodological and sampling issues that may influence reported findings and may reduce the replicability of results across studies. Most importantly, none of these studies considered the possibility that key prefrontal–limbic regions implicated in BD have subregions with structurally and functionally distinct nuclei that interact differentially with other brain networks. Furthermore, the most consistent brain structural[9] and functional[11-13] findings specific to pediatric BD are found in the amygdala. Importantly, however, the amygdala is not homogeneous; it has subregions with structurally and functionally distinct nuclei that have different patterns of connectivity with prefrontal and subcortical networks during the processing of emotional material.[23] In addition, researchers have documented changes in amygdala subregion–cortical functional connectivity from childhood to adolescence[24] that may represent a hierarchical integration of functions across subregions that has implications for the onset of BD during this developmental period.[25] Thus, examining connectivity in amygdala subregions has the potential to significantly advance our understanding of specific patterns of functional connectivity that are implicated in the pathophysiology of BD.

In this study, we examined intrinsic amygdala subregion functional connectivity in post-pubertal youth diagnosed with bipolar I disorder, along key symptom dimensions, within 1 year of these individuals' initial manic episode. Drawing on fMRI findings in the amygdala obtained during rest in adults and youth with BD,[17,18,20,21] we predicted that, compared with healthy youth, youth with bipolar I disorder would exhibit disrupted functional connectivity at rest between amygdala subregions and key brain regions associated with emotion expression and emotion regulation, including the VLPFC, ACC, and insula. We also predicted that these aberrant patterns of connectivity in amygdala subregions would be associated with core symptom dimensions of BD.

METHOD

Participants

The university's panel of medical research in human participants approved this research protocol. After hearing a complete description of the study, parents and youth less than 18 years of age gave written informed consent and assent, respectively; youth aged 18 years or more gave written informed consent. Youth (aged 13–21 years) with bipolar I disorder (n = 20) were recruited either by referral to a pediatric bipolar disorders clinic or from the surrounding community. HC youth (n = 23) without any personal or family history of psychiatric diagnoses or psychotropic medication exposure were recruited through local community advertisements. A telephone screening with a parent established that all participants were fluent in English and did not have any metal in their body, history of head injury (with loss of consciousness of >5 minutes), seizures, or developmental disorders. Youth with BD who were prescribed stimulants did not take them 24 hours before neuroimaging and were required not to have used recreational drugs for at least 30 days before MRI. To avoid the risk of mood destabilization, participants with BD were allowed to continue any other psychotropic medications, including lithium, atypical antipsychotics, anticonvulsants (including valproate, lamotrigine, carbamazepine, and topiramate), and antidepressants.

Assessment of Psychopathology

All participants were administered semistructured clinical interviews to evaluate the presence of past or current psychiatric disorder. Trained interviewers with established symptom and diagnostic interrater reliability ($\kappa > 0.9$) assessed the diagnostic status of all youth by administering the Affective Modules of the Washington University in St. Louis–Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS)[26] and the Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime version (KSADS-PL).[27] Interviewers had previous training and experience with this interview, and administered it separately to the youth and their parents (about the youth) to assess current and lifetime psychiatric diagnoses. Diagnostic decisions were ultimately made by a board-certified child psychiatrist (M.K.S.) and were based on personal interview or discussion with a masters-level research assistant.

Youth in the group with BD were eligible to participate in the study if they met lifetime diagnostic criteria for bipolar I disorder according to both the parent and child WASH-U KSADS and K-SADS-PL. A manic episode was defined by *DSM-IV-TR* criteria that lasted at least 1 week and could not have been precipitated by exposure to recreational drugs, antidepressants, psychostimulants, or other medications or medical conditions. Youth in the HC group were eligible to participate if the following were true: they did not meet criteria for any past or current Axis I disorder based on both the parent and child K-SADS-PL; their parents did not meet criteria for any past or current Axis I disorder by Structured Clinical Interview for *DSM* Disorders; and their first- or second-degree relatives did not meet criteria for an Axis I disorder by Family History Research Diagnostic Criteria.[28]

Symptom severity was assessed on the day of the MRI scan using the Young Mania Rating Scale (YMRS)[29] and the Children's Depressive Rating Scale–Revised (CDRS-R)[30] by raters with established reliabilities (all intrarater, intraclass correlation coefficients [ICCs] >0.9). Core symptoms of mania such as level of disorder insight were derived from specific items in the YMRS and correlated with pertinent imaging findings. Levels of anxiety were assessed by administering the Multidimensional Anxiety Scale for Children (MASC)[31] to the parents. Global functioning was determined using the Children's Global Assessment Scale (CGAS).[32] Levels of impulsivity were assessed by administering the Barratt Impulsiveness Scale (BIS-11) to the youth, which yielded subscale scores on the dimensions of attentional, motor (acting impetuously), and nonplanning (absence of weighing long-term consequences of actions) trait impulsivity.[33] Age, gender, socioeconomic status (Hollingshead Four Factor Index),[34] pubertal stage (Pubertal Development Scale),[35] IQ (Wechsler Abbreviated Scale of Intelligence [WASI]),[36] and handedness (Crovitz Handedness Questionnaire)[37] were also assessed. All demographic and clinical variables were assessed within 1 week of neuroimaging.