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Decreased amygdala–insula resting state connectivity in behaviorally and emotionally dysregulated youth

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ABSTRACT

The Research Domain Criteria (RDoC) adopts a dimensional approach for examining pathophysiological processes underlying categorically defined psychiatric diagnoses. We used this framework to examine relationships among symptom dimensions, diagnostic categories, and resting state connectivity in behaviorally and emotionally dysregulated youth selected from the Longitudinal Assessment of Manic Symptoms study ($n=42$) and healthy control youth ($n=18$). Region of interest analyses examined relationships among resting state connectivity, symptom dimensions (behavioral and emotional dysregulation measured with the Parent General Behavior Inventory-10 Item Mania Scale [PGBI-10M]; dimensional severity measures of mania, depression, anxiety), and diagnostic categories (Bipolar Spectrum Disorders, Attention Deficit Hyperactivity Disorder, Anxiety Disorders, and Disruptive Behavior Disorders). After adjusting for demographic variables, two dimensional measures showed significant inverse relationships with resting state connectivity, regardless of diagnosis: 1) PGBI-10M with amygdala–left posterior insula/bilateral putamen; and 2) depressive symptoms with amygdala–right posterior insula connectivity. Diagnostic categories showed no significant relationships with resting state connectivity. Resting state connectivity between amygdala and posterior insula decreased with increasing severity of behavioral and emotional dysregulation and depression; this suggests an intrinsic functional uncoupling of key neural regions supporting emotion processing and regulation. These findings support the RDoC dimensional approach for characterizing pathophysiologic processes that cut across different psychiatric disorders.

1. Introduction

Psychiatric disorders in youth characterized by behavioral and emotional dysregulation (difficulty regulating the experience and expression of behaviors and emotions) include major depressive disorder (MDD), bipolar spectrum disorders (BPSD), attention deficit hyperactivity disorder (ADHD), anxiety disorders, and disruptive behavior disorders (DBD). These disorders pose diagnostic and treatment challenges due to high comorbidity and the lack of clear biological trait markers (Kowatch et al., 2005; Pavuluri et al., 2005; Arnold et al., 2011, 2012). NIMH Research Domain Criteria (RDoC) offer an alternative approach to identifying transdiagnostic pathophysiologic processes (Cuthbert and Insel, 2013) and biological

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disease markers (Bebko et al., 2014) through dimensions of behavioral and emotional dysregulation.

Neuroimaging techniques examining brain–behavior relationships are ideal for applying RDoC to study pediatric psychiatric disorders. One such technique, resting state functional connectivity (RSC), provides information about intrinsic connectivity in neural networks independent of specific cognitive contexts requiring sophisticated, and often challenging, cognitive tasks which may not represent daily activities. RSC may additionally be more ecologically valid, allowing observation of mind wandering, a commonly occurring activity in the daily lives of youth. In addition, by focusing on neural regions shown to be important in fMRI task-related analyses [such as the amygdala (Altshuler et al., 2005; Foland et al., 2008), striatum (Deveney et al., 2013), prefrontal cortical (Pavuluri et al., 2008; Kalmar et al., 2009; Passarotti et al., 2010; Ladouceur et al., 2011) and anterior cingulate cortical (Gogtay et al., 2007; Kalmar et al., 2009) regions, and an insula-centered neural network supporting salience, interoception, and emotion perception (Rubia et al., 2009; Taylor et al., 2009; Kurth et al., 2010; Cauda et al., 2012; Cloutman et al., 2012)], RSC studies may increase our understanding of pathophysiologic processes in behaviorally and emotionally dysregulated youth.

The small number of RSC studies in youth with behavioral and emotional dysregulation across a variety of psychiatric disorders have used different methods and reported different patterns of abnormal RSC between the amygdala and key prefrontal cortical, anterior cingulate cortical, and insula regions supporting emotion regulation. Using Independent Component Analysis, increased RSC in a neural network comprising the amygdala, orbitofrontal cortex, anterior cingulate cortex, and insula (Wu et al., 2013) in unmedicated, manic, BPSD versus healthy control (HC) youth was reported. In contrast, when using an amygdala seed region, no RSC differences between BPSD and HC (Dickstein et al., 2010) were shown. For youth with MDD, decreases in both amygdala–prefrontal cortical, and amygdala–striatal connectivity were reported relative to HC (Luking et al., 2011). In addition, differences were observed for MDD versus HC youth in RSC between right and left amygdala seed regions with prefrontal gyri (Pannekoek et al., 2014). Additional studies reported both increased (Davey et al., 2012) and decreased (Cao et al., 2006; Cullen et al., 2009; Sun et al., 2012; Pannekoek et al., 2014) RSC between prefrontal and anterior cingulate regions, as well as increased (Gabbay et al., 2013) and decreased (Bluhm et al., 2009; Davey et al., 2012) RSC between striatal and anterior cingulate cortical regions in youth with depression or ADHD versus HC. Together, these findings suggest inconsistent patterns of abnormal RSC in pediatric psychiatric disorders characterized by behavioral and emotional dysregulation.

While the variable nature of these findings may reflect differences in mood state, different analytic techniques, or both, it remains unclear whether there are more consistent patterns of abnormal amygdala-centered RSC associated with specific symptom dimensions across different diagnostic categories. A few studies examined relationships between RSC and symptom dimensions in youth with BPSD or MDD (Luking et al., 2011; Ford et al., 2013; Gabbay et al., 2013; Xiao et al., 2013) but may not represent the wider range of pediatric psychiatric disorders. Furthermore, these studies provided mixed findings of both positive and inverse relationships between mania and depression severity and RSC in networks linking amygdala, striatum, prefrontal, anterior cingulate, and other cortical regions (Luking et al., 2011; Gabbay et al., 2013; Xiao et al., 2013).

In summary, prior studies provide inconsistent reports of RSC among amygdala (Dickstein et al., 2010; Luking et al., 2011), striatal (Bluhm et al., 2009; Davey et al., 2012; Gabbay et al., 2013; Xiao et al., 2013), prefrontal cortical (Cao et al., 2006; Cullen et al., 2009; Dickstein et al., 2010; Davey et al., 2012; Sun et al., 2012; Wu et al., 2013), anterior cingulate cortical (Bluhm et al., 2009; Cullen et al., 2009; Davey et al., 2012; Gaffrey et al., 2012; Gabbay et al., 2013; Wu et al., 2013; Xiao et al., 2013), and insula (Wu et al., 2013) regions in behaviorally and emotionally dysregulated youth. In the present study, we aimed to elucidate for the first time the nature and extent of relationships between pathological dimensions and RSC versus relationships between diagnostic categories and RSC in a clinical cohort of youth with behavioral and emotional dysregulation. Given the central role of the amygdala in emotion processing (Ochsner and Gross, 2005; Phillips et al., 2008) and the inconsistencies shown in the literature, we used an amygdala seed region. We recruited a subset of youth selected from the Longitudinal Assessment of Manic Symptoms (LAMS) study (Horwitz et al., 2010a), a longitudinal, multisite study of youth seeking treatment for behavioral and emotional dysregulation. The LAMS study was designed to assess relationships among the longitudinal course of symptoms, clinical, and functional outcomes in these youth (Section 2). In addition to using DSM-IV classifications of pediatric psychiatric disorders and commonly-used dimensional symptom measures of emotional dysregulation in youth (rating scales of mania, depression, and anxiety), LAMS also uses the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M), a parental report of manic-like behaviors associated with difficulty regulating mood and energy (Section 2) (Youngstrom et al., 2005; Youngstrom et al., 2008).

Primary Hypothesis-Dimensional: As suggested by previous reports of altered RSC in behaviorally and emotionally dysregulated youth implementing dimensional approaches (Luking et al., 2011; Ford et al., 2013; Gabbay et al., 2013; Xiao et al., 2013), we hypothesized that, across all behaviorally and emotionally dysregulated LAMS youth, irrespective of diagnosis, RSC between amygdala, striatum, prefrontal cortices, anterior cingulate cortices, and insula would be significantly associated with dimensional measures of behavioral and emotional dysregulation (PGBI-10M score, mania, depression. and anxiety).

Secondary Hypothesis-Categorical: Based on previous findings of differential patterns of RSC among the above regions between youth with and without specific diagnoses (Dickstein et al., 2010; Luking et al., 2011; Wu et al., 2013), current diagnostic categories in LAMS youth would be differentiated by patterns of amygdala RSC.

In addition, we recruited a comparison group of HC to examine the extent to which significant relationships between RSC and symptom dimensions, or diagnostic categories, represented abnormal RSC in LAMS youth versus HC.

2. Methods

2.1. Description of the Longitudinal Assessment of Manic Symptoms (LAMS) study

LAMS is a longitudinal NIMH-supported study of children and adolescents seeking treatment for behavioral and emotional dysregulation diagnoses such as BPSD, other mood disorders, ADHD, anxiety disorders, and disruptive disorders. Because behavioral and/or emotional dysregulation symptoms similar to manic-like behaviors are common to these disorders, the study name includes reference to "manic symptoms".

The Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M; Supplementary material) was used to screen potential LAMS study participants: 6–12 year old children recruited at their first visit to nine mental health clinics associated with four universities (Findling et al., 2010). The PGBI-10M is parent-rated scale that assesses the child's positive mood and energy dysregulation over the last 6 months and discriminates between BPSD and other comorbidities, such as ADHD (Youngstrom et al., 2005; Youngstrom et al., 2008). High PGBI-10M scores (≥ 12) were common (present in 43% of these youth), regardless of diagnosis, and associated with worse overall functioning and higher rates of a variety of psychiatric disorders, including BPSD, ADHD, disruptive behavior disorders, other mood and anxiety disorders, in the initial screening of the LAMS cohort (Findling et al., 2010; Horwitz et al., 2010b). We invited children scoring ≥ 12 on the PGBI-10M, as well as a demographically matched sample of children who were also seeking mental health care but did not have severe behavioral or emotional dysregulation (scoring ≤ 11), to participate in the study. Independent of diagnosis, high PGBI-10M scores (≥ 12) were associated with worse overall functioning (assessed by the Children's Global Assessment Scale (Shaffer et al., 1983)), higher rates of psychiatric diagnoses (Findling et al., 2010; Horwitz et al., 2010a), and greater prefrontal cortical activity to reward (Bebko et al., 2014). Refer to Horwitz et al. (2010b) for more information on the background and study design of LAMS.