Archival Report

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Longitudinal Relationships Among Activity in Attention Redirection Neural Circuitry and Symptom Severity in Youth

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ABSTRACT

BACKGROUND: Changes in neural circuitry function may be associated with longitudinal changes in psychiatric symptom severity. Identification of these relationships may aid in elucidating the neural basis of psychiatric symptom evolution over time. We aimed to distinguish these relationships using data from the Longitudinal Assessment of Manic Symptoms cohort.

METHODS: Forty-one youth completed two study visits (interscan mean = 21.3 months). Elastic net regression (multiple-response Gaussian family) identified emotional regulation neural circuitry that changed in association with changes in depression, mania, anxiety, affect lability, and positive mood and energy dysregulation, accounting for clinical and demographic variables.

RESULTS: Nonzero coefficients between change in the previously mentioned symptom measures and change in activity over the interscan interval were identified in right amygdala and left ventrolateral prefrontal cortex. Differing patterns of neural activity change were associated with changes in each of the previously mentioned symptoms over time. Specifically, from scan 1 to scan 2, worsening affective lability and depression severity were associated with increased right amygdala and left ventrolateral prefrontal cortical activity. Worsening anxiety and positive mood and energy dysregulation were associated with decreased right amygdala and increased left ventrolateral prefrontal cortical activity. Worsening mania was associated with increased right amygdala and decreased left ventrolateral prefrontal cortical activity. These changes in neural activity between scans accounted for 13.6% of the variance; that is, 25% of the total explained variance (39.6%) in these measures.

CONCLUSIONS: Distinct neural mechanisms underlie changes in different mood and anxiety symptoms over time.

Keywords: Behaviorally and emotionally dysregulated youth, Elastic net, Emotional regulation, Longitudinal, Neural mechanism, Penalized regression

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A goal in pediatric clinical neuroscience is to reveal neural mechanisms underlying development of specific psychopathology that may identify objective neural markers of illness and biological targets to guide treatment choices. This is particularly important for pediatric bipolar spectrum disorders (BPSD), depressive disorders, and attention-deficit/hyperactivity disorder (ADHD), which are often difficult to accurately diagnose and differentiate, largely due to the absence of objective markers, nonspecificity of symptoms, and high comorbidity (1–3). The Research Domain Criteria (RDoC) approach of the National Institute of Mental Health advocates a transdiagnostic, dimensional approach to identify pathophysiologic processes of major psychiatric illnesses. Combined with neuroimaging techniques and longitudinal designs, the RDoC approach can help elucidate neural mechanisms underlying development and progression of specific emotional dysregulation symptoms and behaviors in youth, regardless of diagnoses (4).

The small number of longitudinal neuroimaging studies in youth includes short-term treatment studies of youth with, or at risk for, specific psychiatric disorders (5–14). Studies in youth at risk for BPSD demonstrate that decreased depression severity after divalproex was associated with decreased dorsolateral prefrontal cortical activity during emotion naming (5), whereas decreased mania severity after psychotherapy was associated with increased dorsolateral prefrontal cortical

activity during face emotion gender labeling (6). In youth with BPSD after lamotrigine treatment, decreased depression and mania severity were associated with decreased amygdala activity during emotional rating (10) and decreased amygdala activity during emotional regulation, respectively (7). Additionally, decreased mania severity after lamotrigine in youth with BPSD was associated with increased ventrolateral prefrontal cortical activity during emotional regulation and response inhibition (7,8) and with decreased ventromedial prefrontal cortical activity during affective color matching (9). The very small number of longitudinal studies in youth with ADHD employed attentional rather than emotional regulation tasks and showed decreased insula and putamen activity during task reorientation (11), normalized parietotemporal and cerebellar activation during error processing (12), increased prefrontal activity during cognitive control (15), and increased basal ganglia activity to divided attention (14) with stimulant medication.

Although these longitudinal studies highlight the importance of prefrontal–amygdala activity in emotional regulation and processing, they utilized small sample sizes ($n < 20$) over relatively short intervals and did not assess contributions of variables such as age and sex. Furthermore, these analyses described the impact of treatments on changes in neural activity and behavior. Understanding of neural mechanisms associated with evolution of emotional dysregulation symptoms in youth remains limited.

Studying youth at risk for BPSD requires a transdiagnostic approach, owing to high comorbidity rates of these disorders (1–3,16), frequent conversion to BPSD from major depressive disorder (17), and the variability of symptoms and behaviors over time (18). The Longitudinal Assessment of Manic Symptoms (LAMS) study cohort of behaviorally and emotionally dysregulated youth has a transdiagnostic focus and includes detailed longitudinal symptom, behavioral, psychiatric diagnostic, and neuroimaging assessments.

Additionally, to assess evolution of neural function and symptoms over time, regularized regression analyses such as elastic net, which allow testing large numbers of potential variables, are needed. This class of statistical techniques has been used in genetic studies (19–23) and in clinical research, including functional magnetic resonance imaging (fMRI) (24–26). These techniques minimize risk of inflating model error or overfitting by minimizing the model's mean squared error through cross validation. Our goal in the present study was to examine whether measures of neural activity were associated with improvement or worsening of psychiatric symptoms between two study visits over a 21-month period.

We used a working memory task with emotional distracters that measures redeployment of attention (redirection of attention away from emotional distracters), an emotional regulation subprocess (27,28). This task has been used in studies of adults and youth. The task has been shown to reliably activate prefrontal cortical regions implicated in emotional regulation, and abnormalities in recruitment of prefrontal cortical regions during the task have been demonstrated in mood disordered adults and youth (29–31). Our aim was to test relationships among changes in neural activity over time in regions supporting this emotional regulation subprocess, including amygdala, dorso- and ventrolateral prefrontal, and dorsal anterior cingulate cortices (28,32–34), and longitudinal changes in emotional dysregulation symptoms in LAMS youth. Findings from the small number of previous longitudinal neuroimaging studies in youth, and our cross-sectional findings in LAMS youth showed associations between greater emotional dysregulation severity and lower lateral prefrontal cortical activity during the emotional *n*-back task (EFNBACK), and greater left-middle prefrontal cortical activity to reward (29,35). These findings allowed us to hypothesize that after accounting for clinical and demographic factors, increased amygdala activity, decreased lateral prefrontal cortical activity, and increased left middle prefrontal cortical activity would be associated with worsening emotional dysregulation severity over time, and vice versa.

METHODS AND MATERIALS

Participants

Recruitment was from the LAMS study (hereafter referred to as LAMS-1). One hundred thirty LAMS-1 youth participated in a longitudinal neuroimaging assessment (hereafter referred to as LAMS-2). Eighty-two of the LAMS-2 youth were scanned twice. Youth who successfully completed the first fMRI scanning session (during LAMS-2) were invited to a second scan (LAMS-1 recruitment and exclusion information is described in the Supplemental Methods). Data loss ($n = 41$) was due to sustained head movement greater than 4 mm (2 voxels) during scanning (36), task accuracy less than 75%, and incomplete clinical assessments or task at either scanning visit (Supplemental Table S1). Forty-one of the 82 LAMS youth successfully completed EFNBACK and clinical assessments and had usable data at both scanning sessions. The interscan interval was 21.3 months on average. Youth who completed ($n = 41$), versus youth who did not ($n = 41$), did not differ on clinical or demographic variables (Supplemental Table S1). Institutional review boards approved the study at each site in accordance with the Declaration of Helsinki. Parents/guardians provided written informed consent, and participants provided oral assent.

LAMS youth had several diagnoses, including major depressive disorder, BPSD, ADHD, anxiety disorders, and disruptive behavior disorders (DBD) (Supplemental Table S2). Interviews were conducted by a trained bachelor- or master-level research assistant/associate, followed by consensus meetings with a licensed psychiatrist or clinical psychologist, who confirmed the diagnosis.

Symptom Measures Used as Clinical Outcome Variables

Scan day symptom assessments included parent/guardian reports of positive mood and energy dysregulation using the Parental General Behavior Inventory–10 Item mania scale (PGBI-10M) (37,38) and affective lability using the Child Affect Lability Scale (CALS). For 20 LAMS youth for scan 1, the PGBI-10M was administered near the scan day (mean time between assessment and scan day = 29.2 days). The parent version of the CALS was chosen due to its strong correlation with the Child Behavior Checklist mood lability items (39). Child's report (40) of anxiety was measured with the Screen for