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## Longitudinal relationships among activity in attention redirection neural circuitry and symptom severity in youth

Michele A. Bertocci, PhD<sup>1</sup>, Genna Bebko, PhD<sup>1</sup>, Amanda Dwojak, BS<sup>1</sup>, Satish Iyengar, PhD<sup>2</sup>, Cecile D Ladouceur, PhD<sup>1</sup>, Jay C. Fournier, PhD<sup>1</sup>, Amelia Versace, MD<sup>1</sup>, Susan B. Perlman, PhD<sup>1</sup>, Jorge R. C. Almeida, MD, PhD<sup>12</sup>, Michael J Travis, MD<sup>1</sup>, Mary Kay Gill, MSN<sup>1</sup>, Lisa Bonar, BS<sup>1</sup>, Claudiu Schirda, PhD<sup>1</sup>, Vaibhav A. Diwadkar, PhD<sup>4</sup>, Jeffrey L. Sunshine, MD, PhD<sup>3</sup>, Scott K. Holland, PhD<sup>5</sup>, Robert A. Kowatch, MD, PhD<sup>6</sup>, Boris Birmaher, MD<sup>1</sup>, David Axelson, MD<sup>6</sup>, Sarah M. Horwitz, PhD<sup>7</sup>, Thomas Frazier, PhD<sup>8</sup>, L. Eugene Arnold, MD, MEd<sup>9</sup>, Mary A. Fristad, PhD<sup>8</sup>, Eric A. Youngstrom, PhD<sup>10</sup>, Robert L. Findling, MD, MBA<sup>3,11</sup>, and Mary L. Phillips, MD, MD (Cantab)<sup>1</sup>

<sup>1</sup>Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, University of Pittsburgh

<sup>2</sup>Department of Psychology, University of Pittsburgh

<sup>3</sup>University Hospitals Case Medical Center/Case Western Reserve University

<sup>4</sup>Department of Psychiatry and Behavioral Neuroscience, Wayne State University

<sup>5</sup>Cincinnati Children's Hospital Medical Center, University of Cincinnati

<sup>6</sup>The Research Institute at Nationwide Children's Hospital

<sup>7</sup>Department of Child Psychiatry, New York University School of Medicine

<sup>8</sup>Department of Psychiatry, Ohio State University

<sup>9</sup>Department of Psychiatry and Behavioral Health, Ohio State University

<sup>10</sup>Department of Psychology, University of North Carolina at Chapel Hill

<sup>11</sup>Department of Psychiatry, Johns Hopkins University

<sup>12</sup>Alpert Medical School, Brown University

### 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 (LAMS) cohort.

Corresponding Author: Michele Bertocci, PhD, 121 Meyran Ave, 203 Loeffler Building, Pittsburgh PA 15213.

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**Methods**—Forty-one youth completed two study visits (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**—Non-zero coefficients between change in the above symptom measures and change in activity over the inter-scan 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 above symptoms over time. Specifically, from Scan1 to Scan2, 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 overtime.

### Keywords

neural mechanism; Elastic-net; behaviorally and emotionally dysregulated youth; emotional regulation; longitudinal; penalized regression

## Introduction

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, non-specificity of symptoms, and high comorbidity (1-3). The Research Domain Criteria (RDoC) approach of the NIMH 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), while 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, respectively, were associated with decreased amygdala activity during emotional rating (10)

and decreased amygdala activity during emotional regulation (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 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.

While 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) 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 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; 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, and greater left-middle prefrontal cortical

activity to reward (35,36). 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

### Participants

Recruitment was from the LAMS study (hereafter referred to as LAMS-1). 130 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 (Supplemental Methods describes LAMS-1 recruitment and exclusion information). Data loss (n=41) was due to sustained head movement >4mm (2-voxels) during scanning (37), task accuracy <75%, and incomplete clinical assessments or task at either scanning visit (S1\_Table). Forty-one of the 82 LAMS youth successfully completed the emotional n-back task, 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 (S2\_Table). 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) (S2\_Table). 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) (38,39) and affective lability, using the Child Affect Lability Scale (CALs). For n=20 LAMS youth for Scan1, 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 (40). Child's report (41) of anxiety was also measured, with the Screen for Child Anxiety Related Emotional Disorders (SCARED) (42). Summary scores based on interviewer best judgment of child and parent/guardian reports of manic and depressive symptom severity, respectively, were computed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS) (43), and Depression Rating Scale (KDRS) (44). Change scores (Scan2-Scan1) in these five symptom measures over the interscan interval were dependent variables.

## Paradigm

The emotional n-back (EFNBACK) task is a modified version of the n-back working memory task (45). The EFNBACK task consists of visually presenting a pseudorandom sequence of letters with participants responding to a pre-specified letter. The n-back task includes two memory load conditions: a no-memory load (0-back-e.g., press the button to “M”) and high memory load (2-back-e.g., press the button whenever the current letter is identical to the letter present two trials back (L-X-L)). The emotional n-back task comprises the original n-back task flanked by two emotional or neutral face distracters (46). A no-face condition controls for the interference related to presentation of a face distracter on either side of the letter in 2- and 0-back task conditions. There are eight stimulus blocks: two memory-load conditions (0-back and 2-back), each with one of four emotional face distracter conditions (fearful, happy, neutral or no face distracter). The task comprises three, 7- min 4-sec runs, for a total of 24 blocks- presented in a pseudorandomized order. Each block includes 12 trials. Each trial comprises a letter flanked with either no pictures, or identical pictures of an actor's facial expression (fearful, happy, or neutral). Trial duration is 500ms. The inter-trial interval comprises a fixation cross (flanked with faces), and is jittered (mean duration=3500ms). Participants respond as quickly as possible with their index fingers to the target letter. Instructions are presented on the screen for 4000ms at the beginning of each block. Detailed instructions are provided prior to the scanning session. Our analysis focused on the 2-back with emotional face distracters versus 2-back with no face distracters to allow examination of neural circuitry underlying the ability to direct attention away from emotional distracters during a challenging 2-back working memory activity. Incorrect trials were excluded from the analysis. See S1\_Figure.

## Neuroimaging Data Acquisition and Processing

fMRI data were collected on a 1) 3T Siemens Verio MRI scanner at Case Western Reserve University, 2) 3T Philips Achieva X-series MRI scanner at Cincinnati Children's Hospital, and 3) 3T Siemens Trio MRI scanner at University of Pittsburgh Medical Center. An axial 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (192 axial slices; flip angle=9°; field of view=256 mm; TR=2300 msec; TE=3.93 msec; matrix=256×192) acquired T1-weighted volumetric anatomical images covering the whole brain. A reverse interleaved gradient echo planar imaging (EPI) sequence (210 axial slices; flip angle=90°; field of view=205 mm; TR=2000 msec; TE=28 msec; matrix=64×64) acquired T2-weighted BOLD images covering the whole cerebrum and most of the cerebellum.

Statistical Parametric Mapping software SPM8; <http://www.fil.ion.ucl.ac.uk/spm>) was used to preprocess and analyze fMRI data. Preprocessing involved realignment and unwarping, coregistration, normalization into a standard stereotactic space (Montreal Neurologic Institute, MNI; <http://www.bic.mni.mcgill.ca>) using indirect linear normalization writing unwarped images bounded to include some of the cerebellum, and spatial smoothing using an 8mm FWHM Gaussian kernel. At the first level, global signal normalization was performed to improve model fit assumptions (see Combining data across sites). The jittered ISI design allowed an event related design. Incorrect trials were excluded. In addition, participants were required to perform at >75% accuracy for analysis inclusion. Individual

wholebrain statistical maps were constructed to evaluate conditions of interest. Movement parameters from the realignment stage served as covariates of no interest.

At the second level of BOLD fMRI data analysis, we used the 2back:emotional-face-distracters>2back:no-face-distracters contrast during each scan, as the key measure of redirection of attention away from emotional distracters during n-back task (29). We extracted, at each scan, unthresholded BOLD signal from clusters of activity in anatomic subregions within a single, large anatomical *a priori* mask comprising key emotional regulation subregions: bilateral amygdala, dorsolateral prefrontal cortical (dlPFC; Brodmann Areas (BA) 9 and 46), dorsal anterior cingulate cortex (dACC; BA24/32), and ventrolateral prefrontal cortex (vlPFC; BA47) (28), created from the WFU PickAtlas (WakeForest University, Winston-Salem) (47); Table 1). This step allowed identification of any change in activity per se over the two scans in *a priori* anatomic subregions.

### Combining Data across Sites

We used the following procedures to control for inter-site scanner variability and to combine neuroimaging data across our three sites, as suggested by previous studies (48,49). First, to improve the degree to which the first-level models met model assumptions at each site, global normalization was implemented (35,50). Second, we implemented standards published by the Biomedical Informatics Research Network (BIRN; [www.birncommunity.org](http://www.birncommunity.org)) for data acquisition and information sharing. Using a BIRN phantom, scanner signal-to-noise-ratio (SNR) was collected monthly at each scanner site and monitored for stability (51,52). Third, we included scanning site as a predictor variable in the regularized regression model.

### Analytic plan

Change scores (Scan2-Scan1) were computed for all fMRI and dimensional clinical variables. For our clinical outcome variables, positive change scores indicated higher scores on the Scan2 measurement suggesting worsening over time, while negative change scores indicated lower scores at Scan2 suggesting improvement over time. To improve model fit we standardized the outcome measures. For our neuroimaging predictor variables, positive scores indicated increased activity over time, and negative scores indicated decreased activity over time.

In addition to these neuroimaging and clinical dimensional variables, we included as predictor variables in the model: Scan1 measures of KMRS, KDRS, SCARED, PGBI-10M, and CALS (to control for baseline severity); dichotomous variables of medication (taking/not taking each psychotropic medication class (antidepressants, antipsychotics, mood stabilizers, benzodiazepines, stimulants, and non-stimulant ADHD medications), having/not having a BPSD, major depressive disorder, anxiety disorder, ADHD, substance use disorder, and DBD); behavioral variables of task accuracy and reaction times during the contrast of interest, and demographic variables of site, sex, change in age, age at scan1, handedness, days between scans, and IQ.

We used Elastic-net with the mgaussian family, a penalized least squares regression analysis for variable selection, using the GLMNET package in R(53) (Supplemental Methods). Elastic-net is a modified form of least squares regression that penalizes complex models with a regularization parameter( $\lambda$ ) (54,55) and is sensitive to correlated variables (55). The regularization parameter shrinks coefficients toward zero, and eliminates unimportant terms entirely (53,54,56). Cross validation identifies the optimal penalty term( $\lambda$ ) that minimizes mean cross validated error, reduce the chances of overfitting, and enforces recommended sparsity in the solution (54).

A test statistic for Elastic-net models is still under development (57). We thus report nonzero coefficients identified in the model, the rate-ratio (exponentiated coefficients), and pseudo-r-squared computed from Akaike Information Criteria (AIC) leave-one-out MANOVA regression model analyses. Computing pseudo-r-squared in this way involves comparing the full model loglikelihood with the model containing fewer predictor variables. The difference in these models describes the left-out variables' explained variance.

Supplemental analysis, results, and discussion comparing LAMS youth with healthy control youth can be found in Supplement.

## Results

Elastic-net regression analysis revealed non-zero coefficients over the interscan interval between change in all five emotional dysregulation symptom measures and change in activity in two neural regions: right amygdala and left vIPFC. Specifically, exponentiated parameters showed that, to the main stimulus contrast (2back:emotional-face-distracters>2back:no-face distracter), increased depression, mania, and affective lability severity, but decreased positive mood and energy dysregulation and anxiety severity, were associated with increased right amygdala activity from Scan1 to Scan2 (Figure 1/Table 2). Additionally, increased anxiety, positive mood and energy dysregulation, depression, and affective lability severity, but decreased mania severity, were associated with increased left vIPFC activity during the interval (Figure 1/Table 2). Thus, increased affective lability and depression severity were associated with increased activity in right amygdala and left vIPFC over time; increased anxiety and positive mood and energy dysregulation severity were associated with increased activity in left vIPFC but decreased activity in right amygdala over time; increased mania severity was associated with increased right amygdala and decreased left vIPFC activity over time (Figure 1). Comparing the loglikelihood for each model, the above changes in neural activity between scans accounted for 13.6% of the variance; that is 25% of the total explained variance of 39.6% in our five outcome measures.

Additionally, improvement over time of depression, mania, positive mood and energy dysregulation and affective lability severity, and worsening over time of anxiety severity were all associated with having a BPSD diagnosis at Scan1. Improvement over time of depression, mania, and anxiety severity, but worsening over time of affective lability and positive mood and energy dysregulation severity, was associated with having a DBD diagnosis at Scan1. Improvement over time of depression, anxiety, mania, positive mood and energy dysregulation and affective lability severity were all associated with having higher

task performance accuracy during Scan1. Improvement of depression, anxiety positive mood and energy dysregulation and affective lability severity, and worsening over time of mania severity were associated with having a higher IQ (Table 2).

## Discussion

Elastic-net regression with multiple response Gaussian family identified relationships among longitudinal changes in activity in two neural regions during an emotional n-back task and longitudinal changes in five psychiatric symptom measures over time in LAMS youth. These symptom severity changes included changes in severity of mania symptoms, depression symptoms, anxiety symptoms, affective lability, and positive mood and energy dysregulation. We showed that over 21.3-months, changes in activity in right amygdala and left vIPFC, neural regions involved in redirecting attention away from emotional distracters on the task, were associated with changes in specific affective and anxiety psychopathology in LAMS youth. Furthermore, these neural activity changes between scans explained a fourth (13.6%) of the total explained variance (39.6%) in change in these affective and anxiety symptoms over this time period. These findings are the first, to our knowledge, to indicate that specific patterns of change in activity in neural circuitry important for redirection of attention away from emotional distracters are associated with change in specific symptoms over time in youth recruited transdiagnostically.

During the task, increased left vIPFC activity between scans was associated with increased severity over this interval on four outcome measures: anxiety, depression, affective lability and difficulty regulating positive mood and energy. There is support for this in the literature: non-longitudinal studies showed abnormally elevated left vIPFC activity to reward expectation in adults with bipolar disorder and individuals with higher trait thrill-seeking (58-60). Additionally, in LAMS youth, greater positive mood and energy dysregulation was associated with greater left middle prefrontal activity to reward (35). We recently integrated these non-longitudinal findings into a neural model of predisposition to bipolar disorder (61). Here, abnormally elevated left-sided vIPFC and middle prefrontal cortical activity in emotional contexts, (particularly positive emotional and rewarding), may reflect the role of these regions in decision-making about stimulus-outcome contingencies (59,60,62) and generation of arousal in emotionally-salient situations (63,64). Thus, abnormally elevated activity in these regions in such contexts may reflect higher levels of impulsive sensation seeking and an underlying predisposition to develop bipolar disorder (61). The present study suggests that, over time, increased left vIPFC activity during redirection of attention away from emotional distracters during n-back task performance, may have reflected increased levels of arousal in emotional contexts in LAMS youth, which may have manifested as increased depression, anxiety, affective lability, and increased difficulty regulating positive mood and energy over time. These findings parallel two recent non-longitudinal meta-analyses showing associations between greater emotional dysregulation and greater left vIPFC activity in youth with BPSD (65,66).

Interestingly, and perhaps unexpectedly, *decreased*, rather than increased, mania severity was associated with increased left vIPFC activity over time. However, a similar pattern of decreased mania associated with increased left vIPFC activity, after successful treatment



with lamotrigine, was reported in youth with BPSD (7,8). The authors suggested that decreased vIPFC may be a state marker of mania (7). This may also be related to the mania rating scale used in these analyses. The KMRS is a general rating of mania symptoms used for diagnosing BPSD. This includes symptoms of grandiosity, irritability, and psychosis, not only emotion-related affective symptoms. Collectively, our data thus suggest that, in youth, increased left vIPFC activity over time may be a neural mechanism underlying development of abnormally elevated emotional processing, anxiety and arousal, that are also key symptoms of adult BPSD, but not the development of manic symptoms per se that include a range of symptoms other than emotional processing, anxiety and arousal, e.g., psychosis. Thus, previous findings of elevated left vIPFC activity in adults with BPSD during reward processing (58-60) may reflect high levels of the specific subcluster of emotional processing, anxiety and arousal symptoms in BPSD rather than predisposition to mania per se. Furthermore, given that increased left vIPFC activity between scans was associated with *decreased* mania severity over time, increased left vIPFC activity over time may have conferred some protection against development of the full range of manic symptoms in youth. This may be a reflection of the role of vIPFC in decision-making about stimulus-outcome contingencies (62,67), protecting against development of mania-related symptoms associated with poor decision-making, including psychotic symptoms such as delusions.

Abnormally elevated amygdala activity in mood-disordered youth during emotion processing and emotional regulation has been reported frequently (65,66,68-73), and has long been proposed to be a mechanism for emotional dysregulation (61,74). Our finding of a longitudinal relationship between increased right amygdala activity during redirection of attention away from emotional distracters during n-back task performance and increased depression, mania, and affective lability severity between scans in LAMS youth supports these previous findings, and longitudinal treatment studies showing associations between decreased mania and depression severity and decreased amygdala activity during emotional processing and regulation tasks (7,10).

By contrast, increased positive mood and energy dysregulation and anxiety, (measured with PGBI-10M and SCARED) were associated with *decreased* rather than increased right amygdala activity over time. Interestingly, earlier work by our group showed that youth whose PGBI-10M scores in the five years prior to neuroimaging were high had *lower* amygdala-vIPFC connectivity relative to youth with lower PGBI-10M scores during this time period (36). These findings suggest that the amygdala may not have a major role in the evolution of the cluster of positive mood and energy dysregulation and anxiety behaviors in youth, as measured by child and parental reports. Rather, the above findings suggest that the right amygdala may underlie generation of *negative* emotional affective behaviors associated with threat and salience perception(75) (e.g., anger, sadness, psychotic symptoms) that are included in standardized measures of mania, depression and affective lability. The latter may, however, predispose to longer-term development of anxiety, depressive and psychotic disorders, that are characterized by these symptoms (76,77).

Non-neuroimaging variables were also associated with our five outcome variables. Having a BPSD diagnosis at Scan1 was associated with decreased depression, mania, positive mood and energy dysregulation and affective lability, but worsening anxiety symptoms over time.

Having a DBD diagnosis at Scan1 was associated with improvement in depression, mania, and anxiety but worsening affective lability and positive mood and energy dysregulation. The reason for these findings may be related to medication. Youth with a BPSD diagnosis were more likely to be taking an antipsychotic medication ( $p=.057$ ), potentially resulting in more affective regulation and decreased psychotic symptoms over time, while youth with a DBD diagnosis were less likely to be taking a nonstimulant ADHD medication ( $p=.021$ ), potentially resulting in decreased affective regulation over time (S2&3\_Tables). Higher IQ was associated with decreased depression, anxiety, positive mood and energy dysregulation and affective lability, but with worsening mania severity over time, while higher task accuracy at Scan1 was associated with decreased symptom severity on all five clinical outcome measures over time. These findings suggest that higher cognitive reserve, i.e., higher IQ and greater ability to perform the task, may be protective against worsening psychopathology in youth (78). The relationship between higher IQ and worsening mania severity is more difficult to explain, but parallels previous findings reporting no clear relationship between IQ and development of BPSB (79,80).

Lack of Scan1 pubertal measures is a limitation. Scan2 Pubertal measures were collected, but were not useful without a baseline measurement. Additionally, data loss was a limitation. Participants who did/did not successfully complete both scans did not vary on any demographic or clinical variables, however. While task habituation may be a factor, findings indicate increased activity in cortical and subcortical regions with worsening symptom severity, suggesting that habituation of neural responses did not occur across youth. Future studies should replicate our findings in other samples. While the longer-term relationships among trajectories of symptoms over three or more time points, as described in previous studies of LAMS youth (18,29), and neuroimaging measures remain unknown, we would predict, over a large number of neuroimaging assessments, similar relationships as observed here.

Biological markers that reflect underlying pathophysiological processes are needed to guide and develop novel treatments for pediatric psychiatric disorders. The large longitudinal dataset from the LAMS study of youth with behavioral and emotional dysregulation provided a unique opportunity to examine longitudinal relationships among neural and behavioral changes over time. We show that longitudinal changes in activity in neural regions supporting redirection of attention away from emotional distracters during n-back task performance explained a large portion of the variance in change in five measures of affective and anxiety symptoms over 21.3 months. Our findings suggest distinct neural mechanisms underlying evolution of mania, depression, anxiety, positive mood and energy dysregulation, and affective lability in youth across different diagnoses. This transdiagnostic approach and the differential patterns of observed neural activity- clinical outcome measure relationships, parallel the dimensional approach of the NIMH RDoC, and its focus on examination of specific symptom measures associated with psychopathology. These findings are a step toward identifying specific neural targets, based on understanding of underlying neural mechanisms, to guide treatment choice for specific symptoms associated with behavioral and emotional dysregulation in youth.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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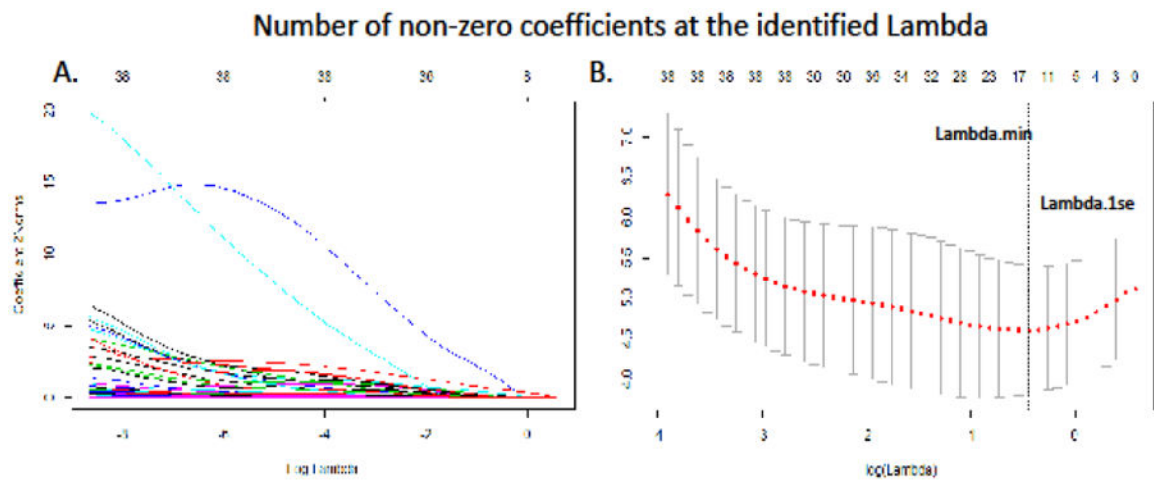
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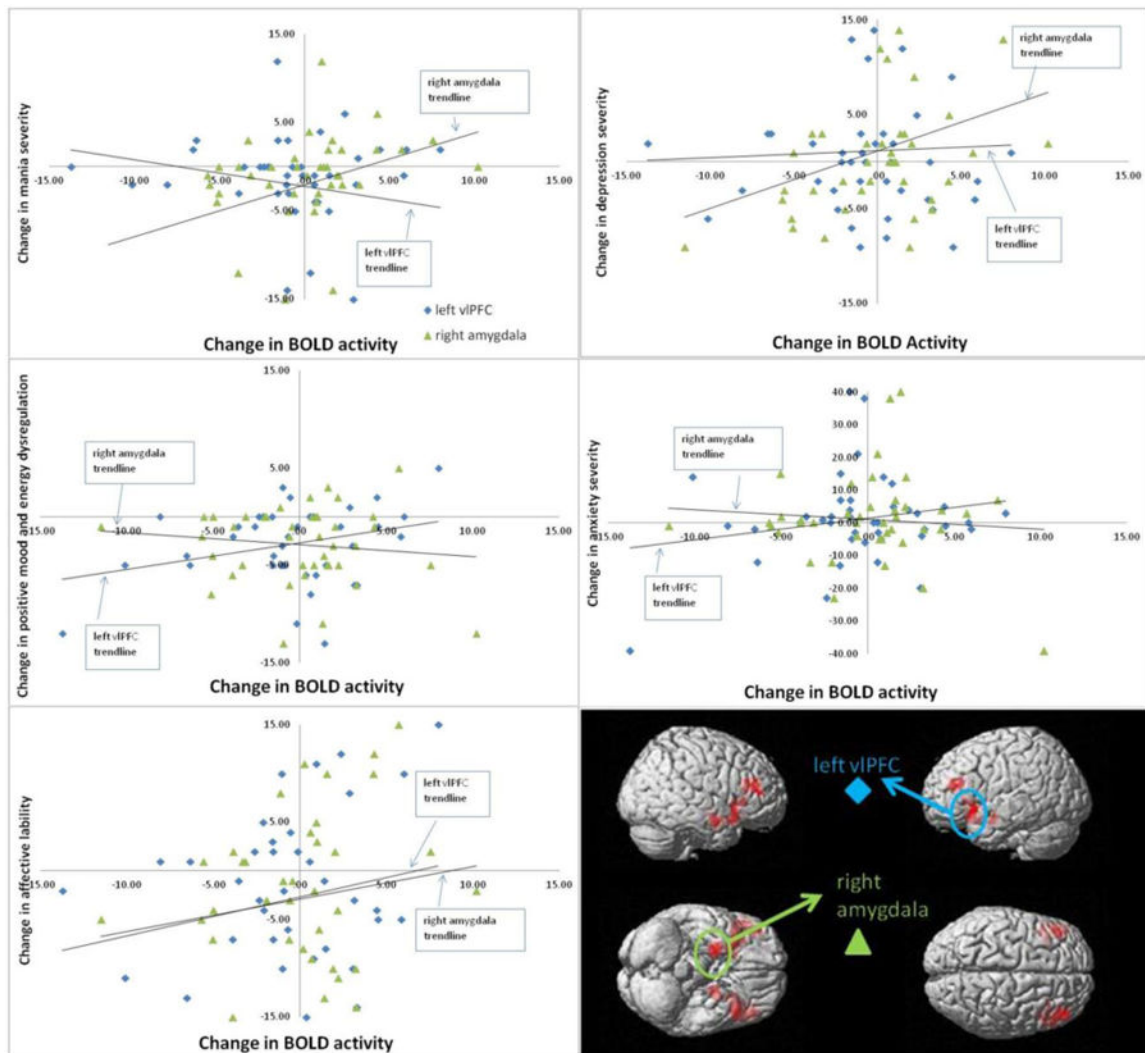
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**Figure 1. Elastic net plots generated in GLMNET**

A. Plot of variable fit. Each curve corresponds to an independent variable in the full model prior to optimization. Curves indicate the path of each variable coefficient as  $\lambda$  varies. B. Plot of non-zero variable fit after cross validation. Representation of the 10-fold cross validation performed in GLMNET that calculates the optimal  $\lambda$ . Lambda.min corresponds to the  $\lambda$  which minimizes mean squared error and was used for variable selection. Lambda.1se corresponds to the  $\lambda$  that is one standard error from the lambda.min.



**Figure 2.**

Relationships between our outcome measures with both right amygdala activity (green triangles) and left ventrolateral prefrontal cortical activity (blue diamonds). Trend lines denote the direction of the relationships. Y axis is the change in clinical outcome measure—a positive change score indicates worsening over time and a negative change score indicates improvement over time. X axis is the change in neural activity— a positive change score indicates increased activity and a negative change score indicates decreased activity. Representation of entire region of interest used in analysis, highlighted regions are right amygdala and left ventrolateral prefrontal cortex areas that show non-zero coefficients with change in five measures of affective dysregulation (depression, mania, anxiety, positive mood and energy, and affective lability) 21.3 months apart.

**Table 1**  
**Unthresholded extracted neural activity during emotional regulation at Scan1 and Scan2**

Contrast of interest: 2back:emotional distracters > 2back:no face distracters unthresholded activity from each region of interest was extracted.

Region	side	BA	K	MNI Coordinates		
				x	y	z
<i>2backemotion&gt;2backnoface</i>						
Amygdala	R	146	18	-4	-22	
Amygdala	L	110	-18	4	-18	
Dorsal Anterior cingulate cortex	R	24/32	1601	4	-4	36
Dorsal Anterior cingulate cortex	L	24/32	1624	-2	-6	36
Ventrolateral prefrontal cortex	L	47	215	-42	14	-8
Ventrolateral prefrontal cortex	R	47	230	26	10	-20
Dorsolateral prefrontal cortex	R	46	130	48	32	14
Dorsolateral prefrontal cortex	L	46	101	-46	30	12
Dorsolateral prefrontal cortex	L	9	475	-56	14	30
Dorsolateral prefrontal cortex	R	9	514	58	6	38

Abbreviations: k = cluster size; MNI=Montreal Neurological Institute coordinate

**Table 2**  
**Exponentiated non-zero coefficients generated from GLMNET using an elastic net regression with multinomial family model**

Exponentiated coefficient is the rate ratio change in the five dependent variables (change in: mania, positive mood and energy dysregulation, depression, anxiety, and affective lability over a 21 month period) corresponding to one unit change in the predictor variable.

Predictor Variable	Exponentiated coefficient				
	Change in mania	Change in positive mood and energy	Change in depression	Change in anxiety	Change in affect lability
Change in right amygdala activity	1.0066	0.9996	1.0106	0.9982	1.0026
Change in left ventrolateral prefrontal cortex activity	0.9996	1.0056	1.0001	1.0001	1.0006
Bipolar spectrum disorder	0.7811	0.7952	0.9830	1.1015	0.8070
Disruptive behavior disorder	0.9201	1.0385	0.9095	0.9453	1.0005
IQ	1.0001	0.9999	0.9999	0.9999	0.9994
Scan1 accuracy	0.9426	0.8300	0.9109	0.9396	0.6988