Original Investigation

Parsing Dimensional vs Diagnostic Category–Related Patterns of Reward Circuitry Function in Behaviorally and Emotionally Dysregulated Youth in the Longitudinal Assessment of Manic Symptoms Study

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IMPORTANCE Pediatric disorders characterized by behavioral and emotional dysregulation pose diagnostic and treatment challenges because of high comorbidity, suggesting that they may be better conceptualized dimensionally rather than categorically. Identifying neuroimaging measures associated with behavioral and emotional dysregulation in youth may inform understanding of underlying dimensional vs disorder-specific pathophysiologic features.

OBJECTIVE To identify, in a large cohort of behaviorally and emotionally dysregulated youth, neuroimaging measures that (1) are associated with behavioral and emotional dysregulation pathologic dimensions (behavioral and emotional dysregulation measured with the Parent General Behavior Inventory 10-Item Mania Scale [PGBI-10M], mania, depression, and anxiety) or (2) differentiate diagnostic categories (bipolar spectrum disorders, attention-deficit/hyperactivity disorder, anxiety, and disruptive behavior disorders).

DESIGN, SETTING, AND PARTICIPANTS A multisite neuroimaging study was conducted from February 1, 2011, to April 15, 2012, at 3 academic medical centers: University Hospitals Case Medical Center, Cincinnati Children's Hospital Medical Center, and University of Pittsburgh Medical Center. Participants included a referred sample of behaviorally and emotionally dysregulated youth from the Longitudinal Assessment of Manic Symptoms (LAMS) study (n = 85) and healthy youth (n = 20).

MAIN OUTCOMES AND MEASURES Region-of-interest analyses examined relationships among prefrontal-ventral striatal reward circuitry during a reward paradigm (win, loss, and control conditions), symptom dimensions, and diagnostic categories.

RESULTS Regardless of diagnosis, higher PGBI-10M scores were associated with greater left middle prefrontal cortical activity (r = 0.28) and anxiety with greater right dorsal anterior cingulate cortical (r = 0.27) activity to win. The 20 highest (t = 2.75) and 20 lowest (t = 2.42) PGBI-10M–scoring youth showed significantly greater left middle prefrontal cortical activity to win compared with 20 healthy youth. Disruptive behavior disorders were associated with lower left ventrolateral prefrontal cortex activity to win (t = 2.68) (all P < .05, corrected).

CONCLUSIONS AND RELEVANCE Greater PGBI-10M–related left middle prefrontal cortical activity and anxiety-related right dorsal anterior cingulate cortical activity to win may reflect heightened reward sensitivity and greater attention to reward in behaviorally and emotionally dysregulated youth regardless of diagnosis. Reduced left ventrolateral prefrontal cortex activity to win may reflect reward insensitivity in youth with disruptive behavior disorders. Despite a distinct reward-related neurophysiologic feature in disruptive behavior disorders, findings generally support a dimensional approach to studying neural mechanisms in behaviorally and emotionally dysregulated youth.

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Pediatric disorders characterized by behavioral and emotional dysregulation, including bipolar spectrum disorders (BPSDs),[1] major depressive disorder,[2,3] attention-deficit/hyperactivity disorder (ADHD),[4-7] disruptive behavior disorders (DBDs),[8,9] and anxiety disorders,[10,11] pose clinical challenges for diagnosis and treatment, particularly because of high comorbidity rates.[12-15] These disorders may thus be better conceptualized as comprising a set of dimensions of behavioral and emotional dysregulation abnormalities that cut across conventionally defined diagnostic categories. This dimensional approach to studying pediatric behavioral and emotional dysregulation parallels the Research Domain Criteria, which aims to elucidate physiologic dimensions reflecting the range of abnormality severity across categorically defined diagnoses.[16]

The Longitudinal Assessment of Manic Symptoms (LAMS) study is an ongoing multisite study of youth with a variety of behavioral and emotional dysregulation diagnoses, several of which include manic-like symptoms (Supplement [eAppendix]). The main purpose of LAMS is to assess relationships among the longitudinal course of symptoms, clinical outcomes, and functional outcomes in these youth. In addition to applying 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 parent self-report dimensional measure of behavioral and emotional dysregulation behaviors in youth that includes measurement of manic-like behaviors associated with difficulty regulating positive mood and energy.[17,18] The PGBI-10M scores were positively and significantly associated with higher scores on the Drive and Fun-Seeking subscales of the Behavioral Activation Scale in youth receiving outpatient services, suggesting that PGBI-10M also captures information regarding reward sensitivity in youth (E.A. Youngstrom, PhD, written communication, December 10, 2012) (Supplement [eAppendix]). Initial screening results from LAMS found that, irrespective of diagnosis, high PGBI-10M scores (≥12; test range is 0-30) were common (in 43% of these youth) and associated with worse overall functioning and higher rates of a variety of psychiatric disorders.[19,20]

To improve understanding of pathophysiologic processes underlying pediatric disorders characterized by behavioral and emotional dysregulation, neuroimaging studies should thus seek to identify (1) neuroimaging biomarkers associated with symptom dimensions characterized by behavioral and emotional dysregulation (eg, mania, depression, anxiety, and PGBI-10M), irrespective of diagnosis, and (2) neuroimaging biomarkers associated with distinct diagnostic categories (eg, BPSD, ADHD, anxiety disorders, DBD). The significant positive associations between PGBI-10M and reward sensitivity measures further suggest that neuroimaging studies of reward processing in behaviorally and emotionally dysregulated youth may, in particular, yield biomarkers of underlying pathophysiologic processes.

Neuroimaging studies in healthy adults highlight key roles of ventral striatum (VS) and different prefrontal cortical regions in reward processing: the VS is activated during changes in expected or obtained reward[21-23]; the orbitofrontal cortex (OFC) (Brodmann area [BA]11) and ventrolateral prefrontal cortex (VLPFC) (BA47) track reward value and arousal during anticipation of rewarding stimuli[24,25]; the dorsal anterior cingulate cortex (dACC) (BA24/32) is involved in attention during reward-related decision making[26]; and the middle prefrontal cortex (mPFC) (BA10) is implicated in risky decision making in potentially rewarding contexts.[27,28] Several studies reported abnormally increased reward sensitivity[29-31] and abnormally elevated reward-related VS,[21,30] OFC, and VLPFC activity[30,32,33] in adults with bipolar disorder. Abnormal reward-related neural activity has also been shown in youth with BPSD[34] as well as in youth with other diagnoses characterized by behavioral and emotional dysregulation, including ADHD,[35,36] anxiety disorders,[37] and DBD.[38,39]

In the present study, we examined a large cohort of LAMS youth. Our primary aim was to identify specific neuroimaging measures associated with the severity of different dimensions of behavioral and emotional dysregulation in these youth irrespective of diagnosis. Our secondary aim was to identify neuroimaging measures associated with distinct diagnostic categories in these youth. We used a number-guessing reward paradigm[40] (win, loss, and control blocks) that has been used in neuroimaging studies of adolescents and adults with mood disorders[30,41] and reliably activates key reward neural circuitry regions: dACC, mPFC, OFC, VLPFC, and VS.[30,42] Using multiple regression analyses, we aimed to evaluate 2 separate hypotheses related to our primary and secondary aims.

Given the above-mentioned studies showing that behaviorally and emotionally dysregulated adults and youth across different diagnostic categories display abnormal prefrontal cortical-VS activity to reward (win vs control) compared with healthy control participants, we developed primary and secondary hypotheses as follows.

Primary Hypothesis (Dimensional)

Across all LAMS youth, irrespective of diagnosis, the magnitude of prefrontal cortical-VS activity to win (>control) would be significantly associated with greater severity of symptoms reflecting behavioral and emotional dysregulation (PGBI-10M, mania, depression, and anxiety).

Secondary Hypothesis (Categorical)

Patterns of prefrontal cortical-VS activity to win (>control) would differentiate current diagnostic categories in LAMS youth. The paucity of studies comparing reward circuitry activity in youth with different diagnostic categories did not allow us to specify the specific patterns of neural activity associated with each diagnostic category.

Control Group

We recruited a comparison group of healthy youth (HY) to examine the extent to which significant relationships between neural activity and symptom dimensions (or diagnostic categories) represented abnormal neural activity in LAMS youth. Again, the paucity of studies on this topic did not allow us to make specific hypotheses.

Methods

Participants

A total of 107 youth (aged 10-17 years) (Supplement [eTable 1]) from the original LAMS study participated in the neuroimaging component of the second phase of the LAMS study. Neuroimaging participants were recruited from 3 LAMS sites: 32 from University Hospitals Case Medical Center/Case Western Reserve University (CWRU), 37 from Cincinnati Children's Hospital Medical Center (CCH); and 38 from University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic (UPMC). The study received institutional board approval at all scan sites. Twenty-two age- and sex ratio–matched HY recruited from all 3 sites (aged 8-16 years) (Supplement [eAppendix]) participated in this study for analyses comparing LAMS youth with HY. Parents/guardians provided written informed consent, and children provided written informed assent prior to study participation. Participants received monetary compensation and a framed picture of their structural neuroimaging scan. Exclusion criteria are reported in the Supplement (eAppendix).

Because of data loss and excessive head movement (>4 mm, as in previous studies[41]) during scanning, data from 22 LAMS youth and 2 HY were excluded, leaving data on 85 LAMS youth and 20 HY youth. In the LAMS group, mean (SD) age was 13.65 (1.96) years (range, 9.89-17.00 years); the sample (CWRU, 25 [29%]; CCH, 31 [36%]; and UPMC, 29 [34%]) included 46 males (54%) (Supplement [eTables 2 and 3]). In the 20 HY group, mean age was 13.31 (2.36) years (range, 8.03-16.92 years); the sample (CWRU, 6 [30%]; CCH, 2 [10%]; and UPMC, 12 [60%]) included 12 males (60%) (Supplement [eTable 2]). Participants excluded for movement were more likely to be male and have lower IQ scores (Supplement [eTable 1]).

Fifty-two (61%) of the 85 LAMS youth were taking at least 1 psychotropic medication (Supplement [eTable 2]). Of those 52 LAMS youth, 29 participants (34%) were taking 1 class of psychotropic medication; 15 youth (18%), 2 classes; 6 youth (7%), 3 classes; and 2 participants (24%), 4 classes. Given ethical problems with stopping medication for research participation, LAMS youth were permitted to use prescribed medications before and on the day of scanning.

Symptom Assessment

Youth in the LAMS group completed several symptom assessment measures. Parents/guardians completed the PGBI-10M (Supplement [eAppendix]) at baseline and 6-month intervals from study entry throughout both phases of LAMS. The PGBI-10M score nearest the scanning session (mean [SD] days between PGBI-10M assessment and scan date, 15.54 [35.01], range, 87 before to 143 days after the scan date) was included as a measure of the most recent PGB1-10M score (Supplement [eTable 2]). The PGBI-10M scores were very stable across 3 assessment points (ie, during 1 year) close to the scan day (Supplement [eAppendix]).

On the scan day, parents and children completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (K-MRS)[43] to assess hypomania and mania severity and the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Episode Depression Rating Scale (K-DRS)[44] to assess depressive symptom severity (Supplement [eTable 2]). Interviewers made final decisions on summary scores based on all available information if parent and child responses differed. Participants completed the Screen for Child Anxiety Related Emotional Disorders (SCARED) on the scan day to assess the youths' anxiety symptoms during the last 6 months (Supplement [eTable 2]).[45]

Diagnostic Categories

This final sample of 85 LAMS youth had a variety of current unmodified *DSM-IV* diagnoses, which were confirmed by a licensed child psychiatrist or psychologist: ADHD (27 [32%]), anxiety disorders (7 [8%]), BPSD (33 [39%]), and DBD (17 [20%]) (Supplement [eAppendix]).

Reward Paradigm

A block-design reward functional magnetic resonance imaging task[40] examined reward-related neural circuitry (**Figure 1**). The Supplement (eAppendix) includes paradigm details.

Neuroimaging Data Analysis

Creation of a Single A Priori Anatomically Defined Bilateral Region of Interest Mask to Test Main Hypotheses

Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England) was used to preprocess and analyze functional magnetic resonance imaging data (Supplement [eAppendix]). Based on previous neuroimaging findings highlighting the roles of many regions in reward processing in healthy adults,[30,33] several anatomically defined regions of interest (ROIs) were selected a priori to be included in a single ROI mask for testing our 2 main hypotheses: dACC (BA24/32), mPFC (BA10), OFC (BA11), VLPFC (BA47), and VS (bilateral spheres centered on the left [−9, 9, −8] and right [9, 9, and −8]; radius = 8 mm based on meta-analyses[46,47]). One anatomically defined bilateral mask containing all 5 of these bilateral individual ROIs was then created from the Wake Forest University PickAtlas[48] for hypothesis testing. By using one large ROI mask, we avoided conducting multiple statistical tests over several small ROIs.

Identifying Neural Activity to Each Stimulus Contrast

After creating the mask, we established which regions in the entire a priori anatomically defined bilateral ROI mask showed significant activity to the 2 different reward task conditions: win > control and loss > control. We ran separate independent 2-tailed *t* tests for each of the 2 contrasts using a voxelwise $P < .025$ to correct for the 2 parallel tests (win > control and loss > control) and a cluster level α of $P < .05$, corrected with a cluster-forming threshold.[49] Significant clusters of activity were then saved as stimulus contrast-related masks for use in the multiple regression analyses used to test hypotheses 1 and 2.

Figure 1. Adapted Reward Task[40]
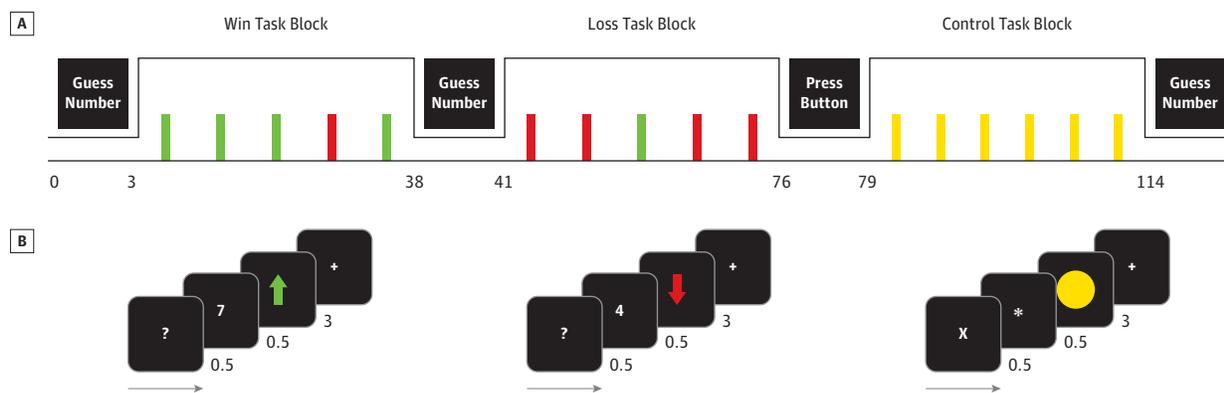
Participants guessed whether a card (value, 1-9) was higher/lower than 5, then viewed the number, outcome (win, green arrow; loss, red arrow), and fixation cross. In control trials, participants pressed a button marked "X," then viewed an asterisk, circle, and fixation cross.

Statistical Approach to Test A Priori Hypotheses

We performed 2 sets of voxelwise multiple regression analyses (1 for each hypothesis) to determine which a priori dimensional (primary hypothesis) and categorical (secondary hypothesis) variables were significantly associated with neural activity to win > control and loss > control after accounting for demographic (age, IQ, and sex), scan site, signal to noise ratio (SNR) (described below), and medication status (taking vs not taking psychotropic medication) variables of no interest. To avoid model overfitting and balance type I and II errors, we adopted the following approach. First, we examined the univariate relationship between each of our variables (ie, variables of interest and variables of no interest) and neural activity using $P < .05$ voxelwise and $P < .05$ clusterwise significance thresholds. Variables that demonstrated a significant relationship were then added to a final multiple regression model containing all such variables. This allowed us to identify variables that remained significant in the final multiple regression model after accounting for all other variables of interest and variables of no interest. This procedure was repeated twice: once for the primary hypothesis involving the 4 dimensional symptom measures (K-DRS, K-MRS, PGBI-10M, and SCARED) and variables of no interest and once for the secondary hypothesis involving diagnostic categories (BPSD, ADHD, DBD, and anxiety disorders) and variables of no interest.

Finally, to determine the extent to which any observed relationships between dimensional measures and neural activity represented abnormalities in neural activity, we compared neural activity of LAMS youth with that of the HY. To do this, we identified the 20 highest- and 20 lowest-scoring LAMS youth on the dimensional measure of interest, and each of these 2 groups was compared with the 20 HY. For these analyses, we examined group differences in neural regions showing the associations between the dimensional measure and neural activity using a voxelwise threshold of $P < .025$ to control for the 2 between-group pairwise comparisons (20 highest-scoring LAMS youth vs HY, and 20 lowest-scoring LAMS youth vs 20 HY; $P < .05$, corrected threshold). All 3 groups were matched on group means for age, IQ, and sex ratio. Comparing the 2 groups of LAMS youth with the HY thereby allowed us to determine whether the pattern of neural activity was associated with the dimensional construct per se (ie, whether the highest-scoring LAMS sample, but not the lowest-scoring LAMS sample, differed significantly from HY in this pattern of neural activity) or was associated with psychopathology more generally (ie, if both LAMS samples differed from HY in this pattern of neural activity).

We conducted similar analyses regarding our secondary hypothesis. That is, when a significant relationship with a diagnostic category was identified in the multiple regression analysis, a follow-up analysis was conducted to further examine the extent to which this represented a pattern of abnormal neural activity vs HY. Here, similar analyses were performed as for our primary hypothesis, but this time comparing the 20 LAMS youth with, as well as 20 LAMS youth without, the diagnosis in question with the 20 HY. Here, all 3 groups were matched on group means for age, IQ, and sex ratio.

Analyses of Multisite Neuroimaging Data: Strategies to Reduce Intersite Signal Variability

We implemented several recommended measures to reduce interscan site variability using global signal normalization in first-level analyses (Supplement [eAppendix]),[50] monitoring scanner signal stability over time (Supplement [eAppendix and eTable 4]), using scan site and SNR as covariates when appropriate (described above), and examining whether the main findings were paralleled by similar patterns of neural activity–behavioral relationships at each site (Supplement [eAppendix and eTable 9]).

Exploratory Analyses

Exploratory whole-brain (voxelwise $P < .001$; clusterwise corrected $P < .05$) analyses were conducted to win > control and loss > control contrasts to determine the extent to which patterns of whole-brain activity to these 2 stimulus contrasts were similar to patterns of neural activity in our a prior bilateral ROI mask.

Results

In all LAMS youth, win > control significantly activated bilateral dACC (BA32), left mPFC, and bilateral VLPFC ($P < .025$, corrected $P < .05$) (**Figure** 2A and **Table** 1). Loss > control significantly activated bilateral dACC (BA32) and right VLPFC ($P < .025$, corrected $P < .05$) (Table 1). Exploratory whole-brain analyses revealed similar activation patterns (Supplement [eTable 5]).

Primary Hypothesis (Dimensional)

Initial univariate analyses revealed that the following symptom dimensional variables showed significant positive relationships ($P < .05$, corrected) with win > control neural activity: PGBI-10M and left mPFC (23 voxels) and SCARED and right dACC (BA32, 20 voxels). For loss > control, no significant relationships with any of the 4 dimensional measures were observed. Thus, we did not perform further analyses for loss > control.

Univariate analyses revealed the following significant relationships ($P < .05$, corrected) to win > control neural activity and variables of no interest: a positive relationship between age and bilateral dACC (left, 25 voxels; right, 22 voxels) and right VLPFC (13 voxels); sex and left dACC (15 voxels) and right VLPFC (35 voxels), with females more than males; and a negative relationship between SNR and right VLPFC (40 voxels). Medication status (taking vs not taking psychotropic medication) was not significantly associated with win > control neural activity.

We added these 3 variables of no interest (age, sex, and SNR) as covariates to a multiple regression model containing the 2 significant dimensional measures (PGBI-10M and SCARED). The 2 relationships between dimensional measures and neural activity observed in univariate analyses remained significant when these 3 covariates were added to the model (both $P < .05$, voxelwise; $P < .05$, corrected within the win > control activity mask): PGBI-10M and left anteriolateral mPFC (20 voxels; Pearson $r = 0.28$, $P = .009$; Spearman $r = 0.23$, $P = .031$ on extracted left anteriolateral mPFC blood oxygen level–dependent signal values) (Figure 2B and C) and SCARED and right ventral dACC (21 voxels; Pearson $r = 0.27$, $P = .011$; Spearman $r = 0.21$, $P = .05$) (Figure 2D and E and **Table** 2). The Supplement (eAppendix) reports associations between the 3 covariates and neural activity from this model.

Regarding the comparison with HY, that group showed significantly less left anteriolateral mPFC activity than did LAMS youth with high PGBI-10M scores (20 voxels: $t_{36} = 2.75$; voxelwise $P < .025$; $P < .05$, corrected; Cohen $d = 0.92$) and LAMS youth with low PGBI-10M scores (11 voxels: $t_{36} = 2.42$; $P < .025$; $P < .05$, corrected; Cohen $d = 0.81$) (**Figure 3** and Supplement [eTable 6]). There were no significant differences in right ventral dACC activity to win > control among the 20 LAMS youth with the highest SCARED score, 20 LAMS youth with the lowest SCARED score, and 20 HY (Supplement [eTable 7]).

Secondary Hypothesis (Categorical)

Initial univariate analyses revealed that of the 3 categorical disorders tests, only DBD showed a significant relationship ($P < .05$, corrected) with significant clusters of activity to win > control in left VLPFC (21 voxels). There were no significant relationships between any diagnostic category and neural activity to loss > control. Thus, we did not perform further analyses of loss > control.

When the 3 variables of no interest showing significant relationships with win > control neural activity described above (age, sex, and SNR) were added to the multiple regression model, youth with DBD continued to show significantly reduced activity ($P < .05$ voxelwise; $P < .05$, corrected within the win > control activity mask) than youth without these disorders in left lateral VLPFC (19 voxels; $t_{83} = 2.68$; $P = .009$; with DBD: mean, −0.40 [0.46]; without DBD: mean, 0.28 [0.35]).

Regarding the comparison with HY, that group had significantly less left lateral VLPFC activity than did either LAMS youth with DBD ($t_{32} = 3.69$; $P < .05$, corrected; Cohen $d = 1.30$) or LAMS youth without DBD ($t_{32} = 3.70$; $P < .05$, corrected; Cohen $d = 1.23$) (Supplement [eTable 8]).

To examine whether the association between DBD and neural activity was independent of the associations between the 2 dimensional measures (PGBI-10M and SCARED), we constructed a final multiple regression model with each of these 3 variables as well as the significant covariates identified above (age, sex, and SNR). The 2 positive relationships between dimensional measures and neural activity remained significant when DBD was added to the model (both $P < .05$, corrected within the win > control activity mask): PGBI-10M and left anteriolateral mPFC (24 voxels), and SCARED and bilateral ventral dACC (left = 13 voxels and right = 21 voxels). Likewise, youth with DBD continued to show significantly reduced activity ($P < .05$, corrected) than did youth without these disorders in left lateral VLPFC (19 voxels).

Discussion

The overall goal of the present study was to identify measures of activity in reward processing neural circuitry that were related to behavioral and emotional dysregulation in a large cohort of youth with several different diagnoses. We aimed to determine the extent to which these neuroimaging measures were associated with either dimensions of behavioral and emotional dysregulation, irrespective of diagnosis, or differentiated diagnostic categories. In support of our dimension-focused primary hypothesis, a greater PGBI-10M score, a stable measure of behavioral and emotional dysregulation within 6 months of scanning, was associated with greater left anteriolateral mPFC activity to win. Greater anxiety on the scanning day was associated with greater right ventral dACC activity to win. In support of our secondary diagnostic category–focused hypothesis, youth with DBD had lower left VLPFC activity to win than did youth without these disorders. These findings remained after including both dimensional measures and DBD in the same multiple regression model and even after accounting for demographic and SNR variables that

Figure 2. Entire Bilateral Region of Interest Mask Analysis to Win > Control in 85 Longitudinal Assessment of Manic Symptoms Youth
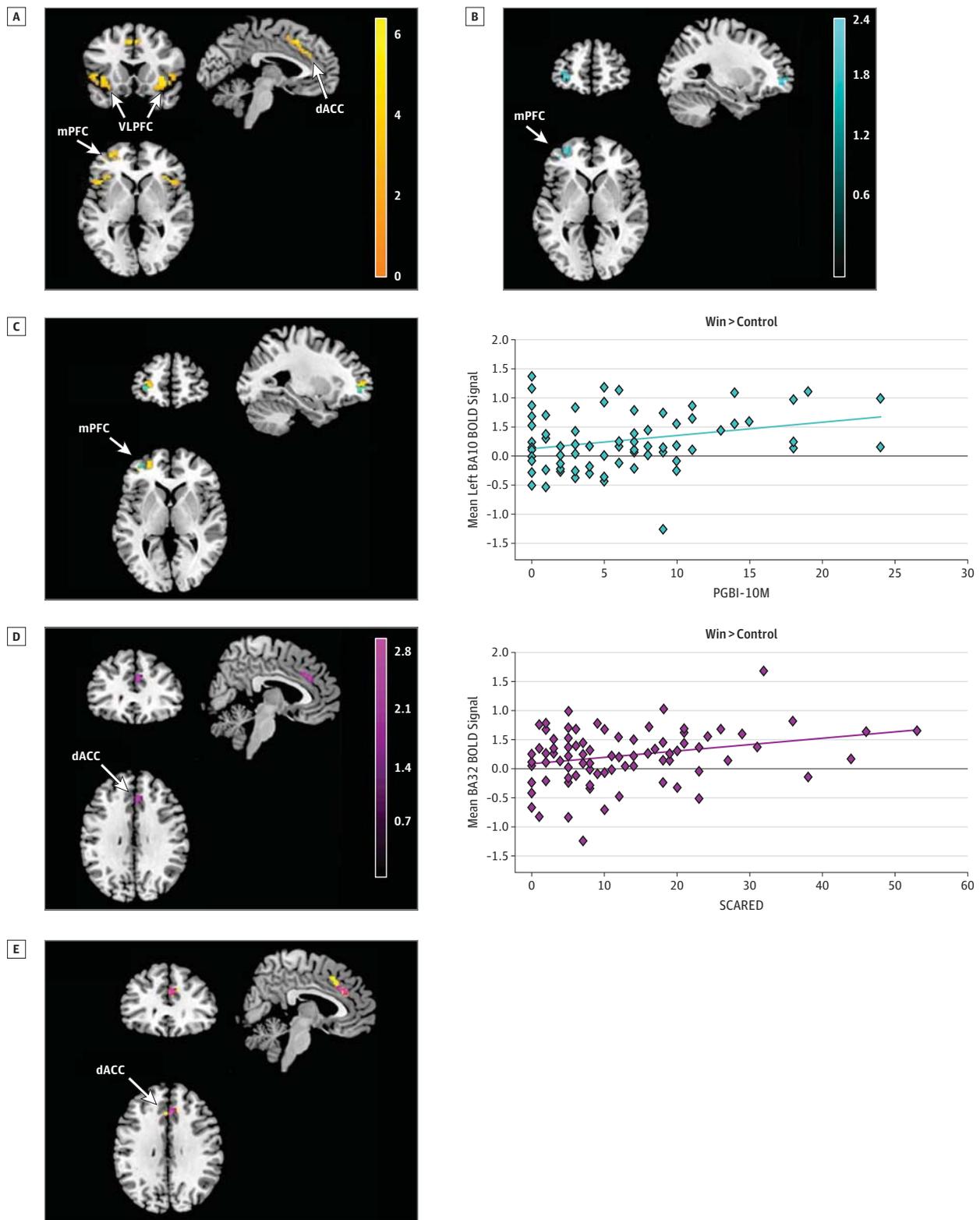
A, Left middle prefrontal cortical (mPFC), bilateral dorsal anterior cingulate cortical (dACC), and bilateral ventrolateral prefrontal cortex (VLPFC) activity (orange). B, Left mPFC activity and Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M) (teal) (r = 0.28). C, Overlap between left mPFC activity in A and B. D, Bilateral dACC activity and Screen for Child Anxiety Related Emotional Disorders (SCARED) (purple) (r = 0.27). E, Overlap between dACC activity in A and D. Markings on color bars indicate t test values; BA, Brodmann area; BOLD, blood oxygen level dependent; and SCARED.

Table 1. Reward-Related Neural Activity in All 85 LAMS Youth[a]

Region	BA	k	MNI Coordinates			Statistic[b]	
			x	y	z	t Test $_{df}$, t_{82}	Uncorrected P Value[c]
Loss > control							
Left dACC	32	76	−6	17	46	5.94	<.001
Right dACC	32	76	3	20	46	5.62	<.001
Right VLPFC	47	24	30	20	−8	4.56	<.001
Win > control							
Left dACC	32	46	−3	20	46	6.16	<.001
Right dACC	32	58	3	20	46	6.35	<.001
Left mPFC	10	38	−39	47	1	5.37	<.001
Left VLPFC	47	56	−45	17	1	4.71	<.001
Right VLPFC	47	57	30	20	−5	5.98	<.001

Abbreviations: BA, Brodmann area; dACC, dorsal anterior cingulate cortex; k, cluster size in voxels; LAMS, Longitudinal Assessment of Manic Symptoms; MNI, Montreal Neurological Institute; mPFC, middle prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

[a] Each row in the table represents the peak voxel within the specified region.

[b] Region of interest analyses using voxelwise P < .025 and P < .05, clusterwise corrected.[49]

[c] Uncorrected voxelwise P value.

Table 2. Symptom Measures Associated With Reward-Related Neural Activity in all 85 LAMS Youth[a]

Region	BA	k	MNI Coordinates			Statistic[b]	
			x	y	z	r Test $_{df}$, r_{79}	Uncorrected P Value[c]
PGBI-10M							
Left mPFC	10	20	−33	53	−2	0.28	.008
SCARED							
Right dACC	32	21	3	32	28	0.27	.002

Abbreviations: BA, Brodmann area; dACC, dorsal anterior cingulate cortex; k, cluster size in voxels; LAMS, Longitudinal Assessment of Manic Symptoms; MNI, Montreal Neurological Institute; mPFC, middle prefrontal cortex; PGBI-10M, Parent General Behavior Inventory 10-Item Mania scale; r, Pearson correlation coefficient; SCARED, Screen for Child Anxiety Related Emotional Disorders (child rating).

[a] Each row in the table represents the peak voxel within the specified region.

[b] Regression analyses of win > control neural activity using voxelwise P < .05 and P < .05, clusterwise corrected.

[c] Uncorrected voxelwise P value.

Figure 3. Group Contrast of Win > Control Activity in Left Middle Prefrontal Cortical (mPFC) Clusters Determined in Analyses Depicted in Figure 2A
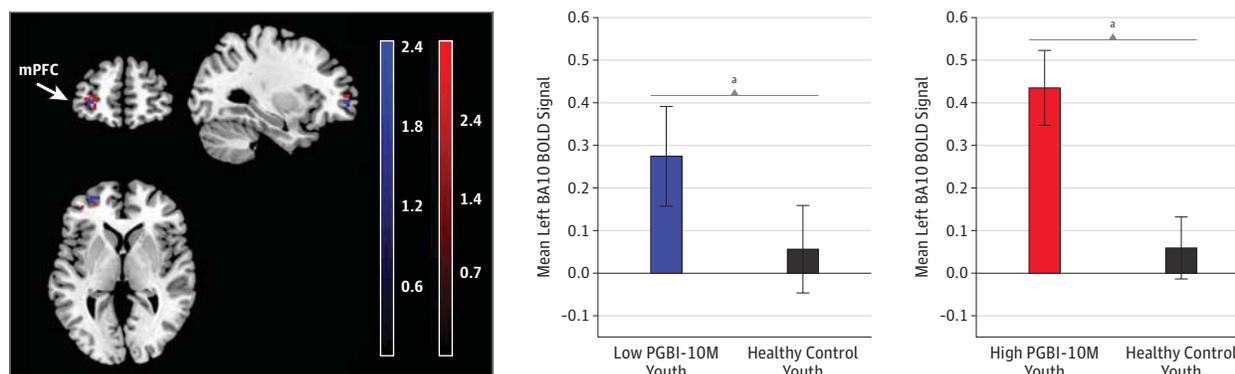
Relative to healthy youth (n = 20) (black) Longitudinal Assessment of Manic Symptoms (LAMS) youth with high Parent General Behavior Inventory 10-Item Mania Scale (PGBI-10M) scores (n = 20) (red) and LAMS youth with low PGBI-10M scores (n = 20) (blue) had greater left mPFC activity. Markings on color bars indicate t test values; error bars, SD. BA indicates Brodmann area; BOLD, blood oxygen level dependent.

[a] Statistically significant difference.

showed significant relationships with win-related neural activity. Overall, LAMS youth activated bilateral dACC to win (>control) and loss (>control), suggesting that LAMS youth attended to both win and loss contexts given the role of the dACC

in attentional processing.[51] Our findings that greater right ventral dACC, part of the ACC affective subdivision,[51] activity to win was associated with greater anxiety suggest that youth with more anxiety may have attended preferentially to win. However, there were no significant right ventral dACC activity differences among high anxious LAMS youth, low anxious LAMS youth, and HY. This may be the result of the greater power of a dimensional rather than a categorical (eg, between-group) approach for detecting brain-behavioral relationships.[52] All LAMS youth also activated bilateral VLPFC to win and right VLPFC to loss, suggesting that both contexts were evaluated as salient given the role of the VLPFC in evaluation of emotionally salient contextual information.[53] The right-sided focus of VPLFC activity to loss may, however, reflect the right hemisphere's role in processing withdrawal-related emotional contexts.[54]

Left mPFC was activated only to win. Given the putative role of the left PFC in approach-related emotion processing,[55] the role of the mPFC in risky decision making in potentially rewarding contexts,[27,28] and the relationship between PGBI-10M and BAS subscales shown in a diagnostically heterogeneous cohort of youth (Youngstrom, personal communication), the positive relationship between left mPFC activity to win and PGBI-10M in LAMS youth suggests that activity in this region may be a biomarker of behavioral and emotional dysregulation and heightened reward sensitivity in rewarding contexts in these youth. Our additional finding that both the 20 LAMS youth with the highest and lowest PGBI-10M scores showed significantly greater left mPFC activity to win than 20 age-, IQ-, and sex-matched HY suggests that elevated left mPFC activity to win may represent an abnormal pathophysiologic process in LAMS youth. These findings parallel those of previous reports[30,33] of elevated left prefrontal cortical activity to reward across different mood-disordered individuals vs healthy control participants and reports[21,30,32] of heightened reward sensitivity in individuals with bipolar disorder. Our present finding thus suggests that elevated left prefrontal activity may reflect heightened sensitivity to reward-related cues and may be a biomarker of pathophysiologic processes associated with behavioral and emotional dysregulation and heightened reward sensitivity across different diagnoses in youth.

Of all diagnostic categories examined, only DBD showed disorder-specific abnormalities in reward circuitry: significantly reduced left VLPFC activity to win in LAMS youth with vs those without these disorders. These findings parallel previous reports of impaired functioning within OFC during reward processing in youth with conduct disorder[38,39] as well as in individuals with higher levels of psychopathic traits.[56,57] Given the role of the OFC and VLPFC in evaluation of reward and emotional contexts, these findings suggest that youth with DBD may evaluate rewarding contexts as less salient than youth without these disorders. This, in turn, may be associated with reduced reward sensitivity and result in the socially inappropriate behaviors characteristic of these youth.[58] Additionally, LAMS youth with and without DBD showed significantly greater left VLPFC activity to win in relationship to age-, IQ-, and sex-matched HY, possibly because both LAMS subgroups had comorbid mood disorders. Further studies are needed to

clarify the extent to which DBD may be associated with impaired functioning in reward circuitry in youth without behavioral and emotional dysregulation.

No significant clusters of activity in VS or OFC were shown by LAMS youth to win, suggesting prefrontal cortical-level attention and evaluative decision-making processing, rather than subcortical-level prediction error encoding or OFC-centered valuation, of reward in these youth. This may reflect the relatively high degree of certainty that participants had of obtaining reward (and thus low levels of prediction error and valuation) during win blocks. Interestingly, mania and depression were not associated with significant activity in a priori ROIs. These findings suggest that elevated left mPFC and bilateral dACC activity during reward processing may represent pathophysiologic processes underlying behavioral and emotional dysregulation, reward sensitivity, and anxiety, but are not associated with the types of behaviors specifically measured by mania and depression rating scales.

There were limitations to the study. We adopted an ROI approach in our analyses, given findings associating activity in specific ROIs during reward processing in healthy individuals.[30,33] Exploratory whole-brain analyses, however, showed that patterns of whole-brain activity to the win and loss contrasts were similar to patterns of neural activity in our a prior bilateral ROI mask. Most (n = 52) participants were receiving medication, and of those, 23 were taking more than one class of psychotropic medication. Although we did not have enough statistical power to assess how using one vs multiple psychotropic medications influenced reward-related neural activity, univariate regression analyses revealed no significant effect of medication status (taking vs not taking psychotropic medication) on win > control neural activity. The use of atypical antipsychotic medication by approximately 27% of LAMS youth (n = 23) may have influenced reward-related neural activity through dopamine receptor blocking.[59] We were unable to specifically examine this relationship, however, because of low statistical power for assessing potential individual medication confounds arising from the use of different types of atypical antipsychotics, which have different neurobiological mechanisms, and interactions between atypical antipsychotics and other classes of psychotropic medications, such as antidepressants, which may also influence dopaminergic activity. We did not include a measure of pubertal status, which has been associated with medial prefrontal activity (dACC)[42] during reward outcome. The next phase of LAMS neuroimaging will include a self-report of pubertal status.[60] Although an event-related design may have been more powerful for identifying interactions between groups and neural activity, our block design may have been more powerful for obtaining robust and statistically powerful neuroimaging findings.[61]

Youth were scanned at multiple sites, but interscanner differences were minimized by monitoring SNR monthly at each scan site using global signal normalization during functional magnetic resonance image processing and including scan site and SNR as covariates in analyses when appropriate. When SNR was included as a covariate, it was associated with a different pattern of neural activity from the main clinical measures of interest (Supplement [eAppendix]). Additionally, neural ac-

tivity–behavioral relationships at each site were very similar to the main dimensional and categorical findings across all sites. The advantages of multisite neuroimaging (increased statistical power and a participant population from a variety of different environments) are likely to outweigh potential limitations. Although the range of PGBI-10M scores (0-24) captured both low and high levels of behavioral and emotional dysregulation in LAMS youth, the mean PGBI-10M score was low (6.09) (Supplement [eTable 1]). Further studies should replicate our findings and aim to examine youth with higher mean scores on this scale. Finally, PGBI-10M scores were not collected for HY, so we were unable to compare scores between the LAMS and HY groups.

There is a pressing need for objective biomarkers reflecting underlying pathophysiologic processes in psychiatric disorders in youth. The large cohort of symptomatically at-risk youth in LAMS provided a unique opportunity to examine the extent to which measures of function within neural circuitry supporting reward processing reflected dimensions of abnormality regardless of diagnosis or was associated with specific diagnostic categories. Our findings support a dimensional approach to the study of neural mechanisms in behaviorally and emotionally dysregulated youth, paralleling the focus of the National Institutes of Mental Health Research Domain Criteria.[16] We also found evidence for distinct neurophysiologic processes during reward processing in youth with DBD. The combination of dimensional and diagnostic categorical approaches may identify biomarkers that can ultimately help identify and guide treatment for youth with, or at risk for, behavioral and emotional dysregulation abnormality.

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