Supplementary Online Content

Bebko GM, Bertocci MA, Fournier JC, et al. Parsing dimensional versus diagnostic category-related patterns of reward circuitry function in behaviorally and emotionally dysregulated youth in the Longitudinal Assessment of Manic Symptoms (LAMS) study.

eText: Supplemental Text

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

LAMS is a longitudinal NIMH-supported study of 6-12 year old children recruited at their first visit to 9 mental health clinics associated with 4 universities(1), seeking treatment for a variety of behavioral and emotional dysregulation diagnoses, including bipolar spectrum disorders (BPSD), other mood disorders, ADHD, anxiety disorders and disruptive disorders. Given that many of these disorders include behavioral and/or emotional dysregulation symptoms similar to manic-like behaviors, the study name, LAMS, included reference to "manic symptoms."

Children were screened with the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M). All children scoring >=12 on the PGBI-10M, and a demographically matched sample of children who scored <=11 who were also seeking mental health care but did not have severe behavioral or emotional dysregulation, were invited to participate. For a more detailed account of the LAMS background and study design, please refer to Horwitz and colleagues(2).

Participants

22 healthy youth (HY) were recruited from all 3 sites [Age: *M*=13.16, *SD*=2.30; 13 males; Case Western Reserve University (CWRU; n=7); Cincinnati Children's Hospital (CCH; n=2); and University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic (UPMC; n=13)].

Exclusion criteria included pregnancy, claustrophobia, metal objects in the body, severe systemic medical illnesses, neurological disorders, history of head trauma with loss of consciousness, using medications with potential CNS effects, IQ<70(assessed by the Wechsler Abbreviated Scale of Intelligence)(3), positive urine drug and/or salivary alcohol screen on scan day, alcohol/substance abuse in the past three months(determined by The Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Life Version with WASH-U mood supplement;K-SADS-PL-W(4)), visual disturbance(<20/40 Snellen visual acuity), inability to complete questionnaires in English, history of physical/sexual abuse, and autistic spectrum disorders/developmental delays.

Symptom Assessment

Unlike ratings of mania, depression, and anxiety, the PGBI-10M is parent-rated, and captures information about positive mood and energy dysregulation over the last six months. The questions/items from the PGBI-10M(5-6) describe positive mood and energy dysregulation and discriminate between BPSD and other comorbidities, such as ADHD. For each question, parents use the following rating scale: 0=Never or hardly ever, 1=Sometimes, 2=Often, 3=Very often or almost constantly. Total PGBI-10M scores can range from 0 to 30. The 10 questions/items and instructions are listed below:

"These are questions about some behaviors that occur in the general population. Think about how often they occur for your child. Using the scale below, select the number that best describes how often your child experienced these behaviors **during the past 6 months.** It does not matter whether or not your child is able to stop these behaviors. So even if your child can stop any of these behaviors, please answer each question according to how often your child experiences them."

1. Has your child experienced periods of several days or more when, although he/she was feeling unusually happy and intensely energetic (clearly more than your child's usual self), he/she was also physically restless, unable to sit still, and had to keep moving or jumping from one activity to another?
2. Have there been periods of several days or more when your child's friends or other family members told you that your child seemed unusually happy or high – clearly different from his/her usual self or from a typical good mood?
3. Has your child's mood or energy shifted rapidly back and forth from happy to sad or high to low?
4. Has your child had periods of extreme happiness and intense energy lasting several days or more when he/she also felt much more anxious or tense (jittery, nervous, uptight) than usual (other than related to the menstrual cycle)?
5. Have there been times of several days or more when, although your child was feeling unusually happy and intensely energetic (clearly more than his/her usual self), he/she also had to struggle very hard to control inner feelings of rage or an urge to smash or destroy things?
6. Has your child had periods of extreme happiness and intense energy (clearly more than his/her usual self) when, for several days or more, it took him/her over and hour to get to sleep at night?
7. Have you found that your child's feelings or energy are generally up or down, but rarely in the middle?
8. Has your child had periods lasting several days or more when he/she felt depressed or irritable, and then other periods of several days or more when he/she felt extremely high, elated, and overflowing with energy?
9. Have there been periods when, although your child was feeling unusually happy and intensely energetic, almost everything got on his/her nerves and made him/her irritable or angry (other than related to the menstrual cycle)?
10. Has your child had times when his/her thoughts and ideas came so fast that he/she couldn't get them all out, or they came so quickly others complained that they couldn't keep up with your child's ideas?

PGBI-10M scores were positively and significantly associated with higher scores on the Drive and Fun-seeking subscales of the Behavioral Activation Scale (BAS; r=0.33 and r=0.25, respectively, $p<0.05$) in 816 youth seeking outpatient services, suggesting that PGBI-10M also captures information regarding reward sensitivity in youth (Youngstrom, personal communication). Initial screening results from LAMS found that, irrespective of diagnosis, high PGBI-10M scores ($\geq$12) were common (present in 43% of these youth). The study also found that higher PGBI-10M scores were 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(1-2).

Stability of PGBI-10M Near to the Scan Day

Assessment of the stability of PGBI-10M over the 5 years preceding neuroimaging assessment was performed using a paired t-test comparing the slope of the first 3 PGBI-10M assessment time points (ie, baseline, month 6, month 12 time points; M=-2.94, SD=2.21) with the slope of the most recent 3 PGBI-10M time points (i.e., the PGBI-10M time point closest to the scan, and the 2 previous PGBI-10M time points; M= -1.12, SD=0.41; paired t-test t(84)=-7.42; $p\leq.001$). The significantly flatter slope of the 3 PGBI-10M assessment time points nearer to the scan date, versus the first 3 PGBI-10M time points, suggest a stabilization of behavioral and

emotional dysregulation among LAMS youth over the course of the first phase of LAMS. Additionally, bivariate correlations of PGBI-10M scores showed less stability from one time point to the next in the first 12 months of data collection with(all *p*s≥.15), while the 3 PGBI-10M scores nearest to scan date were each significantly bivariately correlated (all *p*s≤.001), indicating greater stability of PGBI-10M scores nearer to scan date. *These findings indicate that PGBI-10M scores were extremely stable over the 1 year period (3 PGBI-10M assessment points) nearest to the scan date in all LAMS youth.*

Diagnostic Criteria

The LAMS study used unmodified DSM-IV diagnostic criteria. We defined bipolar spectrum disorders (BPSD) as a diagnosis of bipolar I disorder; bipolar I disorder single episode; bipolar I disorder most recent episode hypomanic; bipolar I disorder most recent episode manic; bipolar I disorder most recent episode mixed; bipolar I disorder most recent episode depressed; bipolar I disorder most recent episode unspecified; bipolar II disorder; bipolar II disorder most recent episode hypomanic; bipolar II disorder most recent episode depressed; subsyndromal bipolar disorder; cyclothymic disorder; or bipolar disorder not otherwise specified. Bipolar spectrum disorder (BPSD) was always documented as a current diagnosis even if it was noted as "in partial/full remission." We defined disruptive behavior disorders as a diagnosis of conduct disorder, disruptive behavior disorders not otherwise specified, or oppositional defiant disorder.

Clinical Characteristics of the LAMS Sample

This final sample of 85 LAMS youth included youth with several different diagnoses. 33 participants had a diagnosis of BPSD and 52 did not have a diagnosis of BPSD. Comorbid diagnoses of the 33 participants with BPSD included anxiety disorders (N=3), ADHD (N=8), and disruptive behavior disorders (DBD) (conduct disorder, oppositional defiant disorder, and disruptive behavior disorder) (N=10). Comorbid diagnoses of the 52 participants without BPSD included comorbid anxiety disorders (N=4), ADHD (N=19), DBD (N=7), and depressive disorders (N=27). The groups necessarily differed on depressive disorder due to the supplanting of a depressive diagnosis by a BPSD diagnosis. Furthermore, the most common diagnosis in LAMS youth without a BPSD diagnosis was a depressive disorder (27/52). The groups (BPSD, non-BPSD) did not differ on comorbid diagnoses of anxiety disorders ($p \geq 1.0$), ADHD ($p \geq .339$), or disruptive behavior disorders ($p \geq .093$).

27 participants had a diagnosis of ADHD, and 58 did not have a diagnosis of ADHD. In participants with ADHD versus those without ADHD there were more comorbid depressive disorders (48% versus 24%; $p < .026$) and DBD (33.3% versus 14%; $p < .038$). The groups (ADHD, non-ADHD) did not differ on BPSD and anxiety disorders. 7 participants had anxiety disorders but did not differ from participants without anxiety disorders on prevalence of comorbid disorders.

17 participants had a diagnosis of a DBD. Participants with DBD had more BPSD (59% versus 34%; $p < .055$) and ADHD (53% versus 27%; $p < .038$) comorbid diagnoses relative to participants without DBD.

Participants with BPSD scored higher on K-MRS ($p = .013$) and PGBI-10M ($p = .003$) than participants without BPSD. There were no differences between BPSD and non BPSD youth on age, IQ, or sex. Participants with BPSD had greater antipsychotic ($p < .001$), mood stabilizer ($p = .020$), and non-stimulant ($p = .02$) medication use than participants without BPSD, although only 6 BPSD youth were taking medications from the latter two classes.

Participants with depressive disorders scored similarly to those without depressive disorders on all clinical rating scales including K-DRS, K-MRS, PGBI-10M , and SCARED. In addition, there were no differences in age or sex between depressive disorder and non depressive disorder youth. Participants with depressive disorders had lower IQ scores than those without depressive disorder($p<.010$).

Participants with ADHD versus those without ADHD scored similarly on K-DRS, K-MRS, and PGBI-10M but those with ADHD scored significantly higher on SCARED ($p<.024$). Participants with ADHD tended to be younger ($p<.057$) but did not differ on IQ or sex to those without ADHD. Medication class use did not differ between the two groups.

Participants with DBD scored significantly higher on K-DRS than those without DBD ($p<.033$). The groups (DND, non-BPD) did not differ on age, IQ, K-DRS score, K-MRS score, PGBI-10M score, SCARED score, or sex. Antipsychotic medication use differed with a greater proportion of youth with DBD taking antipsychotic medication ($p<.011$). No other medication class differed between the groups.

Participants with and without anxiety disorders did not differ on age, IQ, medication use, sex, and clinical measures (K-DRS, K-MRS, PGBI-10M, SCARED).

There were no differences between males and females on age and IQ. More males (54%) were taking stimulants than females (26%; $p<.007$). Males and females did not differ on any other medication class (antidepressants, antipsychotics, benzodiazapines, mood stabilizers, or non-stimulants).

The 3 sites did not differ on key demographic variables of age, IQ, sex, or clinical measures (K-DRS, K-MRS, PGBI-10M, SCARED). Antipsychotic, mood stabilizer, and non-stimulant ADHD medication use was also similar across sites. Antidepressants ($p=.012$) and stimulants ($p=.016$) were used by significantly more participants at CCH than the other 2 sites (eTable1).

Reward Paradigm

For each guessing trial, participants guessed via button press whether the value of a visually presented card (possible value of 1 to 9, but whose value was not yet revealed) would be higher or lower than 5 (3000 msec). Next, the actual numerical value of the card (500 msec) and outcome feedback (Win: green upward-facing arrow; Loss: red downward-facing arrow, 500 msec) were visually presented. After the trial ended, participants viewed a fixation cross (3000 msec intertrial interval). For control trials, participants pressed a button to the letter “X” (3000 msec), then viewed an asterisk (500 msec), yellow circle (500 msec), and fixation cross (3000 msec intertrial interval). The entire reward task lasted approximately 6 minutes.

The paradigm included 9 blocks: 3 win (each comprising 80% win, 20% loss trials), 3 loss (each comprising 80% loss, 20% win trials), and 3 control (no change in earnings) blocks. Control blocks had 6 control trials, while guessing blocks (Win and Loss) had 5 trials in an oddball format with predetermined outcome order (Win block: win, win, win, loss, win; Loss block: loss, loss, win, loss, loss). Participants practiced the task and minimizing head movement in an fMRI simulator before scanning. Although outcome probabilities were fixed, the experimenter led participants to believe that performance would determine outcomes. Throughout practice and scanning, the experimenter verbally encouraged participants to perform to the best of their abilities and to minimize movement.

Neuroimaging Data Acquisition and Analysis

fMRI data were collected on a 1) 3T Siemens Verio MRI scanner at Case Western Reserve University (CWRU), 2) 3T Philips Achieva X-series MRI scanner at Cincinnati Children's Hospital (CCH), and 3) 3T Siemens Trio MRI scanner at the University of Pittsburgh Medical Center (UPMC). An axial 3D magnetization prepared rapid gradient echo (MP-RAGE) sequence (192 axial slices 1 mm thick; flip angle=9°; field of view=256 mm x 192 mm; TR=2300 msec; TE=3.93 msec; matrix=256x192) acquired T1-weighted volumetric anatomical images covering the whole brain. A reverse interleaved gradient echo planar imaging (EPI) sequence (38 axial slices 3.1 mm thick; flip angle=90°; field of view=205 mm; TR=2000 msec; TE=28 msec; matrix=64x64) acquired T2-weighted BOLD images covering the whole cerebrum and most of the cerebellum.

Preprocessing involved realignment, coregistration, segmentation, normalization into a standard stereotactic space (Montreal Neurologic Institute, MNI; http://www.bic.mni.mcgill.ca), and spatially smoothing using a Gaussian kernel (FWHM: 8mm). A two level random-effects procedure was then used to conduct region of interest (ROI) analyses. At the first level individual whole brain statistical maps were constructed to evaluate the main condition contrasts of interest: loss versus control and win versus control. Movement parameters obtained from the realignment stage of preprocessing served as covariates of no interest.

Analyses of multi-site neuroimaging data: strategies to reduce inter-site signal variability

We implemented several recommended measures to reduce inter-scan site variability. First, we used global signal normalization in the first-level analyses for all individuals, as recommended(7), to improve the degree to which first-level model assumptions were met. We calculated the Shapiro-Wilk test of normality of the residuals for each first-level model of the full sample(n=105: 85 LAMS and 20 HY), averaged over the voxels in the functional mask, separately for models that did and did not include global normalization. The Wilcoxon-Mann-Whitney test revealed significant improvement in the normality of residuals for first-level models that included global normalization(Z=2.38,p=.02) at each site. Likely due to reduced power, no individual test for any site met standard thresholds of significance. Second, as recommended by the Biomedical Informatics Research Network(BIRN;standards detailed at http://www.nbirn.net), we monitored SNR monthly using a BIRN phantom at each site to ensure scanner signal stability over time(eTable 4). Third, we used scan site and SNR as covariates when appropriate(described above). Fourth, we determined whether findings testing primary and secondary hypotheses were paralleled by similar patterns of neural activity-behavioral relationships at each individual site. Due to the inevitable loss of power resulting from dividing the sample by three, we conducted exploratory analyses at each site(p<0.05,uncorrected) examining relationships among activity in the entire a priori anatomically-defined bilateral ROI mask and those specific symptom dimensions and diagnostic categories showing neural activity-behavioral- relationships in main analyses(for results, see eText,eTable 9).

Results

Associations between the 3 covariates and neural activity from the dimensional model and the categorical model are presented here.

Primary Hypothesis (Dimensional)

There was a significant positive relationship between age and bilateral dACC (Left: 24 voxels, Right: 25 voxels; Pearson r=0.27, *p*=0.011, Spearman r=0.22, *p*=0.043). Females had significantly greater activity (*p*<0.05, corrected) than males in left dACC (20 voxels; Males: M=0.09, SD=0.35; Females: M=0.35, SD=0.48). There was also a significant negative relationship between SNR and right VLPFC (18 voxels; Pearson r=-0.37, *p*=0.001; Spearman r=-0.32, *p*=.003).

Given that a subset of the PGBI-10M items (questions 1, 2, 6, and 9) was previously shown to discriminate between LAMS youth with high (≥12) versus low (<12) PGBI-10M scores(2), we also performed a multiple regression analysis for Win>control in which we substituted this PGBI-10M subset for the full PGBI-10M variable, and included the same covariates as above. Similar results were obtained (*p*<0.05, corrected): a positive relationship between PGBI-10M subscale and left anteriolateral mPFC (24 voxels; Pearson r=0.28, *p*=0.009, Spearman r=0.21, *p*=0.051); and a positive relationship between SCARED and right ventral dACC (20 voxels; Pearson r=0.28, *p*=.011; Spearman r=0.21, *p*=0.057), the latter just missing significance). (There was no significant relationships between this four-item scale and Loss>control neural activity).

When the PGBI-10M subset was substituted for the full PGBI-10M measure in the model, similar results were found with the 3 covariates. Females had significantly greater left dACC activity relative to males (14 voxels; Males: M=0.08, SD=0.35; Females: M=0.35, SD=0.48). A significant positive relationship was found between age and bilateral dACC (BA32; Left: 25 voxels, Right: 25 voxels; Pearson r=0.28, *p*=0.011; Spearman r=0.22, *p*=0.044) negative relationship was found between SNR and right VLPFC (18 voxels; Pearson r=-0.36, *p*=0.001; Spearman r=-0.32, *p*=0.003).

Secondary Hypothesis (Categorical)

Results revealed a significant positive relationship (p<0.05, corrected) between age and bilateral dACC (Left: 23 voxels, Right: 18 voxels; Pearson r=0.28, *p*=0.01; Spearman r=0.22, *p*=0.04) for Win>control. Females had significantly greater activity (*p*<0.05, corrected) than males in left dACC (15 voxels; Males: M=0.08, SD=0.35; Females: M=0.35, SD=0.47) and right VLPFC (18 voxels; Males: M=0.07, SD=0.45; Females: M=0.36, SD=0.44) to Win>control. There was a significant negative relationship between SNR and activity in right VLPFC (19 voxels; Pearson r=-0.36; *p*=0.001; Spearman r=-0.31, *p*=0.004) to Win>control.

Dimensional and categorical model

Results revealed a significant positive relationship (*p*<0.05, corrected) between age and bilateral dACC (Left: 29 voxels, Right: 25 voxels; Pearson r=0.28, *p*=0.01; Spearman r=0.22, *p*=0.05) to Win>control. Females had significantly greater activity (*p*<0.05, corrected) than males in left dACC (BA32, 14 voxels; Males: M=0.08, SD=0.35; Females: M=0.35, SD=0.46) to Win>control. There was a significant negative relationship between SNR and activity in right VLPFC (19 voxels; Pearson r=-0.35; *p*=0.001; Spearman r=-0.31, *p*=0.004) to Win>control.

Individual site neural activity-behavioral relationships.

Similar patterns of neural activity-behavioral relationships were demonstrated at each individual site as those in our main findings across all sites(eTable 9). Specifically, all three sites showed a significant positive association between PGBI-10M and left anteriolateral mPFC. Two sites showed a significant positive relationship between SCARED and right ventral dACC. Of

the two sites with participants diagnosed with DBD, both showed a significant negative relationship between DBD and left lateral VLPFC(all *p*s<0.05,voxelwise).

Comment

There were additional findings regarding relationships between demographic variables and activity to Win from multiple regression analyses in LAMS youth. Older age was associated with greater activity in bilateral dACC and right VLPFC to Win. This suggests that older LAMS youth may have attended to Win to a greater extent than younger LAMS youth. These findings parallel a previous report of age-related increase in fear-related activity in prefrontal cortex across healthy 8-15 year old youth(8-9). Greater left dACC activity in particular, but also greater right VLPFC activity, was shown by female versus male LAMS youth to Win. The greater dACC activity by females may suggest greater direction of attention to Win by female than male youth. Although the significance of these hemisphere-lateralized findings is unclear, theories implicating the right hemisphere in withdrawal-related emotion processing(10) suggest that the right-lateralized VLPFC finding to Win in females may reflect the fact that Win may have been perceived as a salient emotional context, promoting withdrawal-related percepts in females more than males. These findings are unlikely to be confounds of relationships between age and VLPFC activity given that there were no differences between males and females in age. Although we did not perform multiple regression analyses for the Loss>control contrast, findings from initial correlation analyses showed similar findings for age and sex: older children showed greater left dACC activity, and females showed greater right VLPFC activity. Unique to Loss>control, greater IQ scores were associated with greater right VLPFC activity, suggesting that youth with higher IQ scores may have perceived Loss as more salient than youth with lower IQ scores.

	Total LAMS Sample N=107 M(SD) or Proportion	**Included Participants N=85** M(SD) or Proportion	**Excluded Participants N=22** M(SD) or Proportion	**Statistic Comparing Included vs Excluded Participants**	
Demographic Information					***p* value**
Age	13.39(1.99)	13.65(1.96)	12.38(1.79)	t=-2.76	.915
IQ	100.17(16.46)	102.39(16.93)	91.59(11.16)	t=-3.59	.001**
SES				χ^2=3.05	.550
No/some HS	7/107	4/85	3/22		
GED or HS Diploma	25/107	21/85	4/22		
Some post HS	24/107	18/85	6/22		
Associate's Degree	30/107	25/85	5/22		
Bachelor's Degree or higher	21/107	17/85	4/22		
Sex (males)	62/107	46/85	17/22	χ^2=4.25	.039*
Clinical Measures					
PGBI-10M	6.06(5.82)	6.09(5.73)	5.94(6.28)	t=-0.11	.915
K-DRS	3.79(4.74)	4.24(4.99)	2.00(3.15)	t=-2.61	.012*
K-MRS	4.23(6.97)	4.47 (6.91)	3.32(7.23)	t=-0.69	.492
SCARED	12.30(11.55)	12.44(11.31)	11.73(12.69)	t=-0.26	.896
Current Medication Use					
Antidepressant	18/107	14/85	4/22	χ^2=0.04	.848
Antipsychotic	26/107	23/85	3/22	χ^2=1.71	.191
Benzodiazepine	1/107	0/85	1/22	χ^2=3.90	.048
Mood Stabilizer	8/107	6/85	2/22	χ^2=0.10	.747
Non-stimulant	9/107	6/85	3/22	χ^2=0.98	.322
Stimulant	42/107	36/85	6/22	χ^2=1.67	.197

eTable 1. Demographic information, clinical variables, and current medication usage (Mean ± Standard Deviation or Proportion) describing the LAMS participants included versus excluded from neuroimaging.

Abbreviations: *=significant at p=.05; df=degrees of freedom; F=ANOVA test statistical value; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; K-DRS= Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Episode Depression Rating Scale; K-MRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; M=mean; *p*=*p* value; PGBI-10M=Parent General Behavior Inventory 10 Item Mania Scale; SCARED=Screen for Child Anxiety Related Emotional Disorders (child rating); SD=standard deviation; SES=socio-economic status; t=t-test statistical value; χ^2=chi-squared test statistic value.

	LAMS youth M(SD) or Proportion	Healthy Youth M(SD) or Proportion	Test Statistic (df)	*p* value
Sample Size	85	20		
Demographic Information				
Age	13.65(1.96)	13.31 (2.36)	t(103)=0.68	.50
IQ	102.39(16.93)	108.85 (13.63)	t(103)=-0.46	.65
SES (maternal education)			$\chi^2(4)=7.32$	.12
No/some HS	4/85	0/20		
GED or HS Diploma	21/85	1/20		
Some post HS	18/85	6/20		
Associate's Degree	25/85	5/20		
Bachelor's Degree or higher	17/85	8/20		
Sex (males)	46/85	12/20	$\chi^2(1)=0.23$	.63
Clinical Measures				
PGBI-10M	6.09(5.73)	---		
K-DRS	4.24(4.99)	---		
K-MRS	4.47 (6.91)	---		
SCARED	12.44(11.31)	6.03(7.46)	t(103)=2.42	.018*
Current Comorbid Diagnoses				
ADHD	27/85	0/20		
Anxiety Disorder	7/85	0/20		
BPSD	33/85	0/20		
Depressive Disorder	27/85	0/20		
Disruptive Disorder	17/85	0/20		
Current Medication Use				
Antidepressant	14/85	0/20		
Antipsychotic	23/85	0/20		
Benzodiazepine	0/85	0/20		
Mood Stabilizer	6/85	0/20		
Non-stimulant ADHD	6/85	0/20		
Stimulant	36/85	0/20		

eTable 2. Demographic information, clinical variables, and current medication usage (Mean ± Standard Deviation or Proportion) describing LAMS youth (n=85) and healthy youth (n=20). K-DRS, K-MRS, and PGBI-10M scores were not collected from the healthy youth. Abbreviations: *=significant at p=.05; ADHD=Attention Deficit/Hyperactivity Disorder; BPSD=Bipolar Spectrum Disorder; df=degrees of freedom; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; K-DRS= Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Episode Depression Rating Scale; K-MRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; *p*=*p* value; M=mean; PGBI-10M=Parent General Behavior Inventory 10 Item Mania scale; SCARED=Screen for Child Anxiety Related Emotional Disorders (child rating); SD=standard deviation; SES=socio-economic status – Maternal Education; t=t-test statistical value; χ^2=chi-squared test statistical value.

	Cincinnati M(SD) or Proportion	**Cleveland** M(SD) or Proportion	**Pittsburgh** M(SD) or Proportion	**Test Statistic** (df)	***p***
Sample Size	31	25	29		
Demographic Information					
Age	13.73(1.59)	13.69(2.34)	13.53(2.02)	F(2,84)=0.85	.919
IQ	106.81(14.89)	100.72(20.12)	99.10(15.48)	F(2,84)=1.75	.179
SES (maternal education)				$\chi^2(8)=9.07$	.337
No/some HS	1/31	0/25	3/29		
GED or HS Diploma	10/31	5/25	6/29		
Some post HS	5/31	6/25	7/29		
Associate's Degree	6/31	10/25	9/29		
Bachelor's Degree or higher	9/31	4/25	4/29		
Sex (males)	18/31	13/25	15/29	$\chi^2(2)=0.86$	.307
Clinical Measures					
PGBI-10M	15.00(6.56)	15.36(7.25)	17.59(5.01)	F(2,84)=1.44	.243
K-DRS	4.71(4.31)	3.04(5.06)	4.72(5.38)	F(2,84)=1.03	.363
K-MRS	6.68(8.52)	3.00(5.48)	3.38(5.57)	F(2,84)=2.61	.080
SCARED	14.32(12.15)	9.76(10.35)	12.76(11.09)	F(2,84)=1.15	.322
Current Medication Use					
Antidepressant	10/31	2/25	2/29	$\chi^2(2)=8.85$	.012*
Antipsychotic	12/31	4/25	7/29	$\chi^2(2)=3.81$	.149
Benzodiazepine	0/31	0/25	0/29	---	---
Mood Stabilizer	2/31	2/25	2/29	$\chi^2(2)=0.52$	.974
Non-stimulant	1/31	4/25	1/29	$\chi^2(2)=4.32$	.116
Stimulant	18/31	5/25	13/29	$\chi^2(2)=8.32$	.016*

eTable 3. Demographic information, clinical variables, and current medication usage (Mean ± Standard Deviation or Proportion) describing the LAMS participants from the three neuroimaging sites.

Abbreviations: *=significant at p=.05; df=degrees of freedom; F=ANOVA test statistical value; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; K-DRS= Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Episode Depression Rating Scale; K-MRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale; M=mean; *p*=*p* value; PGBI-10M=Parent General Behavior Inventory 10 Item Mania Scale; SCARED=Screen for Child Anxiety Related Emotional Disorders (child rating); SD=standard deviation; SES=socio-economic status; t=t-test statistical value; χ^2=chi-squared test statistic value.

Scan Site	Scan Date	Signal (M)	Noise (SD)	SNR
UPMC	20110221	888.21	5.39	164.79
UPMC	20110329	914.19	5.28	173.14
CWRU	20110502	882.78	5.00	176.48
UPMC	20110510	901.21	5.57	161.70
CCH	20110506	---------	------	--------
CWRU	20110606	942.02	5.46	172.55
UPMC	20110623	892.69	5.30	168.43
CCH	20110615	---------	------	--------
CWRU	20110704	908.64	5.11	177.85
UPMC	20110712	904.61	5.32	169.88
CCH	20110712	---------	------	--------
CWRU	20110801	946.58	5.24	180.49
UPMC	20110809	808.49	5.56	145.37
CCH	20110809	---------	------	--------
CWRU	20110905	932.04	5.55	168.08
UPMC	20110913	809.69	5.91	137.02
CCH	20110913	---------	------	--------
CWRU	20111003	946.93	6.00	157.92
UPMC	20111010	868.94	5.55	156.54
CCH	20111011	1916.08	11.52	166.30
CWRU	20111107	990.00	5.37	184.45
UPMC	20111108	935.37	5.66	165.36
CCH	20111109	1915.77	12.19	157.12
CWRU	20111205	903.81	5.48	164.91
UPMC	20111213	898.96	5.24	171.62
CCH	20111213	1916.95	11.31	169.43
CWRU	20120102	911.00	4.77	190.99
UPMC	20120110	885.87	5.46	162.25
CCH	20120110	1923.97	11.49	167.45
CWRU	20120206	857.14	4.97	172.61
UPMC	20120214	923.02	5.21	177.12
CCH	20120214	1860.94	12.03	154.73
CWRU	20120305	918.36	5.49	167.28
UPMC	20120313	926.17	4.97	186.35
CCH	20120313	---------	------	--------
CWRU	20120402	896.25	5.21	171.97
UPMC	20120410	899.72	5.63	159.81
CCH	20120426	1911.94	12.77	149.77

eTable 4. Monthly signal-to-noise ratio values for the BIRN phantoms at each scan site.

Signal-to-noise (SNR) is calculated by dividing the mean of the scanner signal by the standard deviation of the scanner noise. Abbreviations: ----=No data available; CCH=Cincinnati Children's Hospital; CWRU=Case Western Reserve University; M=mean; SD=standard deviation; SNR=signal to noise ratio; UPMC=University of Pittsburgh Medical Center

		MNI Coordinates				
Region	**Laterality/ BA**	**k**	**x**	**y**	**z**	**Test Statistic (df**
Loss>control						
Frontal lobe / Medial frontal gyrus / Anterior cingulate gyrus	L8/R9/L32	421	-6	17	49	t(82)=6.09
Occipital lobe	R30	319	12	-73	10	t(82)=6.08
Inferior parietal lobe	L40	267	-39	-52	43	t(82)=5.99
	R40	203	45	-52	49	t(82)=5.65
Middle and superior temporal gyrus	R21/R22	63	48	-31	-5	t(82)=4.61
Posterior insula		82	-30	17	-8	t(82)=4.37
		83	30	17	-8	t(82)=4.59
Posterior cingulate gyrus	R23	54	0	-28	19	t(82)=4.45
Superior frontal gyrus	L6	52	-27	2	55	t(82)=4.44
Win>control						
Medial frontal gyrus / Anterior cingulate gyrus	R9/R32	394	3	23	46	t(82)=6.94
Inferior parietal lobe	L40	377	-39	-55	43	t(82)=6.88
	R40	307	45	-52	49	t(82)=6.67
Inferior frontal gyrus / Ventrolateral prefrontal cortex	L45/47	196	-48	17	4	t(82)=5.20
	R45/R47	214	30	23	-5	t(82)=6.62
	L6/L9	281	-39	8	52	t(82)=6.25
Posterior cingulate gyrus	L23	115	6	-28	22	t(82)=6.02
Middle prefrontal cortex	L10	185	-36	47	1	t(82)=5.37
Frontal lobe / Medial frontal gyrus	R8/R9	374	42	26	43	t(82)=5.06

eTable 5. Whole brain activity to each stimulus contrast.

Each row in the table represents the peak voxel within the specified region, $p<0.001$, uncorrected voxelwise; $p<0.05$, clusterwise corrected. Abbreviations: BA=Brodmann area; df=degrees of freedom; k=cluster size in voxels; L=left; MNI=Montreal Neurological Institute coordinates; *p*=uncorrected voxelwise *p* value; R=right; t=t-test statistical value.

	Highest PGBI-10M Youth M(SD) or Proportion	Lowest PGBI-10M Youth M(SD) or Proportion	Healthy Control Youth M(SD) or Proportion	Test Statistic (df)	*p* value
Sample Size	20	20	20		
Demographic Information					
Age	13.32(2.06)	13.87(1.77)	13.31(2.36)	F(2,59)=0.47	.625
IQ	99.90(18.32)	106.80(15.61)	104.25(13.63)	F(2,59)=0.95	.391
SES (maternal education)				$\chi^2(6)=8.41$	.210
No/some HS	0/20	0/20	0/20		
GED or HS Diploma	6/20	5/20	1/20		
Some post HS	4/20	4/20	6/20		
Associate's Degree	8/20	6/20	5/20		
Bachelor's Degree or higher	2/20	5/20	8/20		
Sex (males)	10/20	11/20	12/20	$\chi^2(2)=0.40$	.812
Clinical Measures					
PGBI-10M	14.35(4.80)	0.25(0.44)	----	t(19.33)=13.07	<.001**
Neural Activity		**MNI Coordinates**		**Statistic**	
Left mPFC (BA 10)	k	x	y	z	Test Statistic (df)	$p_{uncorrected}$
High PGBI-10M Youth>Healthy youth	20	-36	50	4	t(36)=2.75	0.005*
Low PGBI-10M Youth>Healthy youth	11	-27	53	-5	t(36)=2.42	0.010*

eTable 6. Demographic information (Mean ± Standard Deviation or Proportion) and neural activity comparing the twenty LAMS youth with the highest PGBI-10M scores, twenty LAMS youth with the lowest PGBI-10M scores, and twenty healthy youth.

Each row in the neural activity part of the table represents the peak voxel within the specified region. The clusters of neural activity reported met criteria for AlphaSim correction. Abbreviations: **=significant at $p \leq .001$; *=significant at $p \leq .010$; BA=Brodmann area; df=degrees of freedom; F=ANOVA test statistical value; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; *p*=*p* value; k=cluster size in voxels; MNI=Montreal Neurological Institute coordinates; mPFC=middle prefrontal cortex; $p_{uncorrected}$=uncorrected voxelwise *p* value; PGBI-10M=Parent General Behavior Inventory 10 Item Mania Scale; SES=socio-economic status; t=t-test statistical value; χ^2=chi-squared test statistic value.

	Highest SCARED Youth M(SD) or Proportion	Lowest SCARED Youth M(SD) or Proportion	Healthy Control Youth M(SD) or Proportion	Test Statistic (df)	*p* value
Sample Size	20	20	20		
Demographic Information					
Age	13.30(2.08)	14.24(1.93)	13.31(2.36)	F(2,59)=1.28	.285
IQ	100.80(14.73)	99.65(14.58)	104.25(13.63)	F(2,59)=0.56	.575
SES (maternal education)				$\chi^2(8)=10.30$	.245
No/some HS	1/20	0/20	0/20		
GED or HS Diploma	4/20	5/20	1/20		
Some post HS	4/20	5/20	6/20		
Associate's Degree	9/20	6/20	5/20		
Bachelor's Degree or higher	2/20	4/20	8/20		
Sex (males)	8/20	12/20	12/20	$\chi^2(2)=2.14$	.343
Clinical Measures					
SCARED	28.85(9.82)	1.6(1.47)	6.03(7.46)	F(2,59)=83.22	<.001*

eTable 7. Demographic information (Mean ± Standard Deviation or Proportion) comparing the twenty LAMS youth with the highest SCARED scores, twenty LAMS youth with the lowest SCARED scores, and twenty healthy youth.

Abbreviations: *=significant at $p \leq .001$;; df=degrees of freedom; F=ANOVA test statistical value; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; *p*=*p* value; SCARED=Screen for Child Anxiety Related Emotional Disorders (child rating); SES=socio-economic status; t=t-test statistical value; χ^2=chi-squared test statistic value.

	Disruptive Disorder Youth	Non-Disruptive Disorder Youth	Healthy Control Youth	Test Statistic (df)	*p* value
	M(SD) or Proportion	M(SD) or Proportion	M(SD) or Proportion		
Sample Size	16	20	20		
Demographic Information					
Age	13.27(2.12)	13.31(1.93)	13.31(2.36)	F(2,55)=.002	.998
IQ	97.50(14.90)	100.80(17.71)	104.25(13.63)	F(2,55)=0.84	.436
SES (maternal education)				$\chi^2(8)=22.63$	.004*
No/some HS	3/16	0/20	0/20		
GED or HS Diploma	5/16	3/20	1/20		
Some post HS	1/16	7/20	6/20		
Associate's Degree	5/16	9/20	5/20		
Bachelor's Degree or higher	2/16	1/20	8/20		
Sex (males)	8/16	9/20	12/20	$\chi^2(2)=0.93$	.628
Neural Activity		**MNI Coordinates**		**Statistic**	
Left VLPFC (BA 47)	k	x	y	z	Test Statistic (df)	$p_{uncorrected}$
Disruptive Disorder Youth>Healthy youth	19	-51	17	-5	t(32)=3.69	<.001**
Non-Disruptive Disorder Youth>Healthy youth	23	-42	20	1	t(36)=3.70	<.001**

eTable 8. Demographic information (Mean ± Standard Deviation or Proportion) and neural activity comparing the sixteen LAMS youth with disruptive behavior disorders, twenty LAMS youth without disruptive behavior disorders, and twenty healthy youth.

Each row in the neural activity part of the table represents the peak voxel within the specified region. The clusters of neural activity reported met criteria for AlphaSim correction. The disruptive disorder group and non-disruptive disorder group did not significantly differ from each other on SES. Abbreviations: **= significant at $p \leq .001$; *=significant at $p \leq .005$; BA=Brodmann area; df=degrees of freedom; F=ANOVA test statistical value; GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; k=cluster size in voxels; MNI=Montreal Neurological Institute coordinates; $p_{uncorrected}$=uncorrected voxelwise *p* value; SES=socio-economic status; t=t-test statistical value; VLPFC=ventrolateral prefrontal cortex;;χ^2=chi-squared test statistic value.

			MNI Coordinates			Statistic	
	Lat/ BA	**k**	**x**	**y**	**z**	**Test Statistic (df**	***p***
PGBI-10M and mPFC							
CCH	L10	17	-33	41	22	t(29)=3.65	.001
CWRU	L10	7	-27	53	-5	t(23)=2.69	.006
UPMC	L10	6	-45	41	13	t(27)=2.07	.024
SCARED and dACC							
CCH	L32	27	-9	23	28	t(29)=2.84	.004
	R32	29	6	32	28	t(29)=3.18	.002
CWRU	L32	0					
	R32	0					
UPMC	L32	30	-3	26	-8	t(27)=3.10	.002
	R32	97	3	32	-8	t(27)=2.86	.004
Disruptive behavior disorders and VLPFC						t(82)=6.02	<.001
CCH	L47	24	-36	32	-8	t(29)=2.71	.006
UPMC	L47	31	-33	17	-8	t(27)=3.89	<.001

eTable 9. Main neural activity-behavioral relationships identified in hypothesis one and two at each scan site.

Each row in the table represents the peak voxel within the specified region. No LAMS youth at CWRU were diagnosed with disruptive behavior disorders. Abbreviations: BA=Brodmann area; CCH=Cincinnati Children's Hospital; CWRU=Case Western Reserve University; dACC=dorsal anterior cingulate cortex; df=degrees of freedom; F=ANOVA test statistical value; k=cluster size in voxels; L=left; Lat=Laterality; MNI=Montreal Neurological Institute coordinates; mPFC=middle prefrontal cortex; *p*=uncorrected voxelwise *p* value; PGBI-10M=Parent General Behavior Inventory 10 Item Mania Scale; R=right; SCARED=Screen for Child Anxiety Related Emotional Disorders (child rating); t=t-test statistical value; UPMC=University of Pittsburgh Medical Center; VLPFC=ventrolateral prefrontal cortex.

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