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Predicting clinical outcome from reward circuitry function and white matter structure in behaviorally and emotionally dysregulated youth

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Abstract

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Behavioral and emotional dysregulation in childhood may be understood as prodromal to adult psychopathology. Additionally, there is a critical need to identify biomarkers reflecting underlying neuropathological processes that predict clinical/behavioral outcomes in youth. We aimed to identify such biomarkers in youth with behavioral and emotional dysregulation in the Longitudinal Assessment of Manic Symptoms (LAMS) study. We examined neuroimaging measures of function and white matter in the whole brain using 80 youth aged 14.0(sd=2.0) from 3 clinical sites. Linear regression using the LASSO method for variable selection was used to predict severity of future behavioral and emotional dysregulation [measured by the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M)] at a mean of 14.2 months follow-up after neuroimaging assessment. Neuroimaging measures, together with near-scan PGBI-10M, a score of manic behaviors, depressive behaviors, and sex, explained 28% of the variance in follow-up PGBI-10M. Neuroimaging measures alone, after accounting for other identified predictors, explained approximately one-third of the explained variance, in follow-up PGBI-10M. Specifically, greater bilateral cingulum length predicted lower PGBI-10M at follow-up. Greater functional connectivity in parietal-subcortical reward circuitry predicted greater PGBI-10M at follow-up. For the first time, data suggest that multimodal neuroimaging measures of underlying neuropathologic processes account for over a third of the explained variance in clinical outcome in a large sample of behaviorally and emotionally dysregulated youth. This may be an important first step toward identifying neurobiological measures with the potential to act as novel targets for early detection and future therapeutic interventions.

Keywords

youth; behavioral and emotional dysregulation; prediction; fMRI; diffusion imaging

Introduction

Increasingly, neuroimaging studies are identifying biomarkers reflecting underlying neuropathologic processes that are predictive of clinical outcomes in adults.(1) Studies have shown, for example, that measures of neural structure and function can predict response to psychotherapy and psychotropic medications in adults with major depressive disorder (MDD) and anxiety disorders (AnxD). (2–4) In studies of youth with MDD, neural activity predicted response to CBT (5) as well as magnitude of depressive symptoms one to two years after neuroimaging assessment. (6, 7) In youth with AnxD, neural activity measured by fMRI (8) and Evoked Response Potentials (ERP) (9) predicted improvement in anxiety symptoms. Although still a nascent research field, the latter studies indicate feasibility of neuroimaging to identify measures of neural function reflecting underlying neuropathologic processes that, over and above clinical and demographic measures, predict future behavioral outcomes in youth with psychiatric disorders. Larger sample sizes, multimodal neuroimaging techniques, and sophisticated statistical analyses that allow testing of a large number of potential predictor variables are needed to fully examine the extent to which combinations of measures of neural structure and function along with clinical, demographic, genetic, and environmental factors predict future outcomes in youth. LASSO (Least Absolute Shrinkage and Selection Operator) regression is one such statistical technique that has been adopted for use in genetic studies (10–14) and is gaining favor in clinical research

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including fMRI (15, 16). This technique allows for testing of a large number of potential predictor variables, relative to the number of study participants, while minimizing model error and minimizing the risk of overfitting.

The goal of the present study was to identify measures of neural function and structure predicting future behavioral and emotional dysregulation in a large group of youth in the Longitudinal Assessment of Manic Symptoms (LAMS) study. LAMS is an ongoing multi-site study examining longitudinal relationships among the course of symptoms, outcomes, and neural mechanisms associated with different clinical trajectories, in youth with symptoms characterized by behavioral and emotional dysregulation. (17, 18) It is ideally suited as a platform study in which to identify neuroimaging measures predicting future levels of behavioral and emotional dysregulation in youth.

A novel feature of LAMS is that it adopts both a conventional diagnostic (categorical) and a symptom (dimensional) approach to characterize severity of psychiatric symptoms and underlying neural mechanisms in youth. The latter approach supports the NIMH's Research Domain Criteria (RDoC) (19) and expectations, (20) aiming to elucidate neuropathologic processes associated with dimensions of psychopathology that cut across different diagnostic categories, which in turn may help identify neurobiological markers that predict future outcome. One dimensional measure of behavior employed in LAMS is the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M), a parental report of behavioral and emotional dysregulation in youth that specifically captures behaviors associated with difficulty regulating mood and energy. (21, 22) In LAMS youth, PGBI-10M scores were elevated across multiple diagnostic categories (17, 18) and predicted clinical outcome. (23) Furthermore, we previously reported in LAMS youth relationships between functional and white matter structural abnormalities in neural circuitry supporting reward processing and emotional regulation with dimensional and categorical measures of affective pathology. (24, 25) This neural circuitry comprises prefrontal cortical, striatal, and insula regions (25) and white matter tracts connecting these prefrontal cortical and subcortical regions, including uncinate fasciculus, cingulum, and forceps minor. (26) Given the above cross-sectional associations among these neuroimaging measures, PGBI-10M, affective pathology, and outcome,(23) these neuroimaging measures are promising candidate neural predictors of future levels of behavioral and emotional dysregulation, and the present longitudinal study sought to test these predictive associations, 14.2 months later.

We hypothesized that in LAMS youth, future behavioral and emotional dysregulation, measured by follow-up PGBI-10M, would be predicted by: 1) neural function, measured by the magnitude of both activity and functional connectivity (FC), in prefrontal-cortical-striatal reward circuitry; and 2) diffusion imaging (DI) measures of white matter structure in tracts across the whole brain, but especially in the tracts supporting emotion processing noted above. Given that outcome has been consistently predicted by stability of psychopathology and by demographic factors such as age, (23, 27, 28) we also aimed to determine the relative proportion of future behavioral and emotional dysregulation predicted by neuroimaging, over and above clinical and demographic measures.

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Methods

Participants

We recruited 130 youth (9–18 years; Table 1) with a variety of symptoms and diagnoses from three LAMS sites [Case Western Reserve University (n=32); Cincinnati Children's Hospital (n=48); University of Pittsburgh Medical Center (n=50)] to participate in the neuroimaging component of the LAMS second 5-year period (LAMS-2). Participants from the first 5-year period (LAMS-1) were selected to include approximately equal numbers from each site: 1) with high (≥12) versus low (<12) PGBI-10M scores; 2) who were older (≥13 years) versus younger (≤12 years) on scan day; 3) who were male versus female. Institutional Review Boards approved the study at each site. Parent/guardian consent and child assent were obtained.

Clinical Assessments

Assessments used in this analysis included parent/guardian's reported PGBI-10M, (21, 22) which has shown good reliability and diagnostic discrimination (21, 22) and the Depression Rating Scale (KDRS) (29) and Mania Rating Scale (KMRS) (30) supplements from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version with supplemental questions from Washington University (K-SADS-PL-W), a well validated clinician interview with good psychometric properties. (29) Psychiatric diagnoses were confirmed by a licensed psychiatrist or psychologist and included bipolar spectrum disorder (BPSD), major depressive disorder (MDD), Anxiety disorder (AnxD), ADHD, and disruptive behavior disorder (DBD); frequency of diagnoses are reported in Table 1.

PGBI-10M scores were obtained on or near the day of scan (TIME1) and at follow-up interviews [(mean=14.2 months (range: 4.8–23.7)] after neuroimaging scans (TIME2). TIME1:PGBI-10M and TIME2:PGBI-10M scores differed significantly ($t(79) = 2.13$, $p = .036$) [TIME1:PGBI-10M: mean(SD) =5.96(5.95), TIME2:PGBI-10M= 4.59(5.2)] and were only moderately correlated $r = .47$.

Exclusion Criteria

Exclusion criteria were: systemic medical illnesses, neurological disorders, history of trauma with loss of consciousness, use of central nervous system effecting non-psychotropic medications, IQ<70 assessed by the Wechsler Abbreviated Scale of Intelligence (WASI), positive drug and/or alcohol screen on the day of MR scan, alcohol/substance abuse in the past 3 months (determined by the K-SADS-PL-W), significant visual disturbance, non-English speaker, autistic spectrum disorders/developmental delays, pregnancy, claustrophobia, and metal in the body. Participants were excluded for excessive head movement,(31) data acquisition artifact, incomplete data acquisition, and follow-up nonattendance (n=50), leaving 80 LAMS youth (Age=9.89–17.7). Excluded youth were younger, had lower IQ, were more likely to have a DBD, and had lower maternal education (Table 1).

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Reward Task Description

Measures of reward-related neural activity were acquired using a validated, approximately six minute, block-design card guessing reward task. (31) For each guessing trial, participants guessed via button press whether the value of a card shown on the screen would be higher or lower than 5 (3000 msec) (possible value of 1 to 9, but whose value was not yet revealed). Next, the card's actual value was presented (500 msec) and outcome feedback was presented (Win: green upward-facing arrow; Loss: red downward-facing arrow, 500 msec). After each trial, a fixation cross was presented (3000 msec intertrial interval). Control trials consisted of participants pressing a button to the letter "X" (3000 msec). They then viewed an asterisk (500 msec), yellow circle (500 msec), and fixation cross (3000 msec intertrial interval).

The paradigm included 9 blocks: 3 win (80% win, 20% loss trials), 3 loss (80% loss, 20% win trials), and 3 control (constant in earnings) blocks. Control blocks had 6 control trials, while guessing blocks (Win and Loss) had 5 trials in an oddball format with preset outcome order (Win block: win, win, win, loss, win; Loss block: loss, loss, win, loss, loss). Participants practiced the task and practiced minimizing head movement in an fMRI simulator before scanning. Outcome probabilities were fixed, however the experimenter led participants to believe that performance determined outcomes. Participants were encouraged to both perform well and to stay as still as possible.

Neuroimaging Data Acquisition and Processing

fMRI data were collected on a 1) 3T Siemens Verio MRI scanner at CWRU, 2) 3T Philips Achieva X-series MRI scanner at CCH, and 3) 3T Siemens Trio MRI scanner at 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 × 192 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 (38 axial slices 3.1 mm thick; 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.

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). The detailed preprocessing stream is described in supplemental materials. A two level random-effects procedure was then used to conduct whole brain analyses. At the first level individual whole brain statistical maps were constructed to evaluate the main condition contrasts of interest: win versus control. Movement parameters obtained from the realignment stage of preprocessing served as covariates of no interest.

Psychophysiological Interaction Methodology

Given the key role of the ventral striatum (VS) in reward processing, we used a VS (bilateral spheres ±9,9,-8; radius=8mm (32, 33)) seed region to examine FC between VS and reward-related wholebrain activity during the Win>Control contrast, using Psychophysiological Interaction (PPI) analysis. After processing the Reward task as above, we extracted

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associated VS suprathreshold clusters as the seed region and created a PPI vector by multiplying the mean time series from the seed region by task condition vectors. Next, we ran single subject first level analyses for each task condition using 3 primary regressors: PPI vector, time course vector, and task condition vector were created, controlling for movement parameters.

Diffusion Imaging (DI) Methodology

DI data were collected in the same scanning session as fMRI data at the above three sites, and were processed using ExploreDTI, Freesurfer and Tracts Constrained by Underlying Anatomy (Tracula) software. (34) White matter tracts were automatically reconstructed using probabilistic tractography accounting for anatomy (see supplemental materials). DI analysis is sensitive to diffusivity of water in white matter tracts in the brain. In white matter tracts with axons that have densely packed collinear fibers, water diffuses along the principal/longitudinal axon but in non-collinear axons (crossing fibers), water moves along two or more directions. Measures include axial diffusivity; Lambda1 (L1; diffusivity along the principal axis); radial diffusivity (RD; diffusivity along directions perpendicular to the longitudinal axis); length and volume of tracts. Tracts with densely-packed collinear axons are characterized by high L1; tracts with non-collinear axons are characterized by high RD; while white matter damage is characterized by high RD. Measures of fractional anisotropy (FA) were not included, as these were not independent of L1 and RD measures for a given tract, as FA is computed as the ratio between L1 and RD.

Combining Data Across Sites

Merging neuroimaging data from multiple sites is feasible given the use of appropriate measures.(35, 36) To control for inter-site scanner variability and to combine neuroimaging data across our three sites we performed the following. First, we implemented global normalization to improve the degree to which first-level models met model assumptions at each site(37). Second, the Biomedical Informatics Research Network (BIRN; http://www.nbirn.net) standards for data acquisition and information sharing were implemented. Scanner signal-to-noise-ratio (SNR) was collected using a BIRN phantom and monitored for stability monthly at each scanner site (36, 38). Third, we used scanning site as a predictor variable in all relevant statistical models.

Neuroimaging IVs

1) Functional measures—Significant wholebrain mean BOLD activity to the Win>Control contrast was extracted (voxelwise $p \leq .001$, clusterwise 3DClusterSim $p \leq .05$ corrected; Table 2, minimum $k=38$) as recommended (39–43). Full weight half max (FWHM) x, y, and z smoothing parameters used in 3DClusterSim were acquired from the SPM 2nd level output. Similarly for PPI, significant whole brain parameter estimates were extracted from regions showing significant positive modulation of functional connectivity with the VS seed to the Win>Control contrast (voxelwise $p \leq 0.05$, clusterwise 3DClusterSim $p \leq 0.05$ corrected, minimum $k=134$) as in previous studies. (44–46) These mean activity and functional connectivity measures were included as predictor variables.

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2) Structural measures—We chose two orthogonal measures of white matter structure: longitudinal diffusivity (L1), radial diffusivity (RD), plus volume, and length. These measures were extracted from all major tracts connecting prefrontal, parietal, temporal, and subcortical regions in the whole brain, including bilateral tracts of the anterior thalamic radiation, cingulate angular bundle, cingulum, inferior longitudinal fasciculus, parietal superior longitudinal fasciculus, temporal superior longitudinal fasciculus, uncinate fasciculus, forceps major and forceps minor. We additionally included the corticospinal tract as a control reference tract.

Data Analytic Plan

The TIME2:PGBI-10M was not distributed normally [range=0–23, mean=4.59 (5.2), median=3.0], and residuals calculated from initial Ordinary Least Squares models were likewise non-normal. Residuals appeared to follow a Poisson distribution; therefore, to model TIME2:PGBI-10M data we used methods assuming a Poisson distribution. Because we had data with more variables than observations, we used a LASSO regression analysis for data selection and reduction using the freely available GLMNET package in R(47). LASSO is a modified form of least squares regression that penalizes complex models with a regularization parameter (λ).(48) This penalization method shrinks coefficients toward zero, and eliminates unimportant terms entirely(47–49), thereby minimizing prediction error, reducing the chances of overfitting, and enforcing recommended sparsity in the solution(48).

GLMNET uses a quadratic approximation to the loglikelihood (an outer Newton loop) and then cyclical coordinate descent algorithm (50, 51) that is computed along a regularization path (an inner weighted least squares loop) to optimize the penalized loglikelihood; this is programmed in FORTRAN. Cyclical coordinate descent refers to optimization of each parameter separately, holding all others fixed until coefficients stabilize. Regularization is the process of adding constraints to a problem to avoid over fitting. Regularization in GLMNET for a Poisson regression is performed by producing the path of tuning parameters (λ) and solving the following equation over the range of λ, thereby identifying the optimal λ.

$$\min_{\beta_0\beta} -\frac{1}{N} l(\beta|X,Y)+\lambda\left((1-\alpha)\sum_{i=1}^{N}\beta_i^2/2+\alpha\sum_{i=1}^{N}|\beta_i|\right)$$

GLMNET uses cross validation to identify the optimal penalty term (λ) that would minimize the mean cross validated error for our model and guard against Type III errors (testing hypotheses already suggested by the data). We used a k=10 fold cross validation approach.

A test statistic or p-value for LASSO that has a simple and exact asymptotic null distribution was proposed by Lockhart(52), but has not yet been rigorously tested for conventional use or implemented in standard statistical packages. We thus report non-zero coefficients identified in the model, the rate ratio (exponentiated coefficients), and pseudo r-squared computed from Akaike Infromation Criteria (AIC) of standard leave-one-out Poisson regression model analyses. The leave-one-out procedure involves comparing the full model (all appropriate

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predictor variables) with the model containing fewer predictor variables (removing the predictor variables of interest). The difference in these models is the explained variance of the left-out variables.

For our analysis, TIME2:PGBI-10M scores served as the outcome variable, and TIME1:PGBI-10M, in addition to other TIME1 clinical and demographic variables acquired on or near scan-day (TIME1), were predictor variables. TIME1 measures included the above BOLD, functional connectivity, and DI neuroimaging measures, TIME1:PGBI-10M, KMRS, KDRS scores, and diagnoses (ADHD, BPSD, MDD, DBD, AnxD), age, IQ, sex, medication status (taking versus not taking each psychotropic medication class: stimulant, non-stimulant ADHD, mood stabilizer, antipsychotic, and antidepressant psychotropic medications), scan site, and days between TIME1:PGBI-10M and TIME2:PGBI-10M.

Results

Seven predictors together optimized model fit using the minimum λ identified by cross validation. This minimum λ corresponds to the penalty at which minimal mean squared error (MSE) is achieved(47). Of these, three were clinical variables (TIME1:PGBI-10M, KMRS, and KDRS scores), one was sex, and three were neuroimaging variables (right and left cingulum length, and VS-right parietal connectivity. Table 3).

Exponentiated parameters indicated that greater values of right and left cingulum length predicted lower TIME2:PGBI-10M (i.e., better behavioral and emotional regulation). By contrast, greater VS-parietal functional connectivity, higher TIME1:PGBI-10M, being female, higher TIME1:KMRS, and TIME1:KDRS predicted higher TIME2:PGBI-10M scores (i.e., worse behavioral and emotional dysregulation).

A pseudo r-squared of .28 was calculated for the standard Poisson model containing seven non-zero predictors identified from the LASSO regression model versus an intercept only model, indicating that 28% of the TIME2:PGBI-10M variance was explained by the model. Leave-one-out analysis showed that three neuroimaging variables (right and left cingulum length and VS-right parietal functional connectivity) explained 10% of the TIME2:PGBI-10M variance, and four clinical and demographic variables (TIME1:PGBI-10M, TIME1:KMRS, TIME1:KDRS, and sex) explained 15% of the TIME2:PGBI-10M variance.

Discussion

Our goal was to assess the ability of multimodal neuroimaging measures to predict future levels of behavioral and emotional dysregulation in psychiatrically-unwell youth. We used a LASSO regression model, along with cross-validation, an approach that penalizes complex models with a regularization parameter and identifies the parameter that minimizes the mean squared error, sending unimportant coefficients to zero. Findings indicated that 28% of the variance in a key measure of behavioral and emotional dysregulation, PGBI-10M score, measured at a mean of 14.2 months after neuroimaging assessment was predicted by bilateral cingulum length and VS-right parietal functional connectivity, together with TIME1:PGBI-10M score, TIME1:KMRS score, TIME1:KDRS score, and sex. Our

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conservative analytic approach revealed that neuroimaging measures alone, even after accounting for other significant predictors, predicted 10% of the variance, ie., approximately one-third of the explained variance, in this outcome measure.

We show here that greater FC between VS and parietal cortex, components of neural circuitry supporting reward processing, (53–56) predicted worse future behavioral and emotional dysregulation. Greater activity in this VS-parietal neural circuitry to reward cues and outcomes has been reported in individuals with substance use disorders, and greater severity of behavioral and emotional dysregulation.(53, 55) These findings suggest that neuroimaging measures of a key underlying neuropathologic process in bipolar disorder, heightened reward sensitivity,(57) may predict worse future behavioral and emotional dysregulation in psychiatrically-unwell youth. Our findings further indicate that the magnitude of functional connections among different reward circuitry regions, reflecting more global measures of functioning in this circuitry, rather than activity within specific regions of this circuitry, contribute to future outcome.

By contrast, better future behavioral and emotional regulation was predicted by greater bilateral cingulum length. Most DI studies of adults and youth with BPSD or subthreshold symptoms reported altered FA and RD in key WM tracts implicated in emotion regulation, including the cingulum. (58, 59) Our findings are the first to our knowledge, however, to suggest that greater cingulum length may be associated with capacity for better future behavioral and emotional regulation in youth. Given that the cingulum has projections within subcortical regions and sends long association projections between prefrontal cortex and other cortical areas,(60) including, along with the superior longitudinal fasciculus, connections to key prefrontal and parietal cortical regions implicated in attentional control, (61, 62) longer cingulum tract length may increase capacity for attentional control that, in turn, may confer protection against future worsening of behavioral and emotional dysregulation.

Non-neuroimaging measures also predicted future behavioral and emotional dysregulation. Greater TIME1:PGBI-10M predicted worse future behavioral and emotional dysregulation. Given that this is a repeated measure, this is likely an indication of the measure's consistency over time. It was thus necessary to adjust for the baseline score to clarify effects of other predictor variables. Additionally, TIME1:KMRS and TIME1:KDRS scores predicted worse future behavior and emotional dysregulation. These scores, although not highly correlated with TIME1:PGBI-10M ($r<.48$ and .19 respectively), are measures of mood dysregulation, and would thus also be likely to predict future mood dysregulation, as measured by TIME2:PGBI-10M. They also incorporate the youth's perspective and clinical observations of youth behavior, in addition to the parent perspective captured in the PGBI-10M. Finally, sex showed a non-zero coefficient in the LASSO model, with being female associated with worse future behavioral and emotional regulation, consistent with the well-established increase in risk for depression among females in adolescence and early adulthood.

Diagnoses did not predict TIME2:PGBI-10M, suggesting that, in support of the RDoC approach, measures of symptom dimensions, rather than diagnostic categories, may better

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reflect underlying neuropathologic processes in psychiatric illness. This was despite the use of standardization in the LASSO regression model, which assigns the same scale to all variables, thereby consistently penalizing each variable(63). Overall, our findings are aligned with one of the few neuroimaging predictor studies in youth (10–16 years) with anxiety disorders,(8) in which 36% of variance in outcome Clinical Global Impressions-Severity (CGI-S) score, was predicted using a combination of near-scan:CGI-S and left amygdala activity. This amount of explained outcome variance in this study was similar to that predicted by the combination of neuroimaging and clinical measures in the present study. The explained variance in outcome predicted by neuroimaging alone was not reported in this previous study, however.

There were limitations. We focused on whole brain reward neural circuitry and white matter tracts. Including other neuroimaging measures, such as gray matter volumes or cortical thickness, may improve future outcome predictions. (We report findings in supplemental materials from an additional LASSO model that included measures of cortical thickness, along with the neuroimaging, clinical and demographic measures included in the present LASSO model, as predictors). We assumed a linear model with a Poisson distribution due to evidence of linear growth in white matter volume among youth in this age group (64). Nonlinear models may also be considered in future studies. We used standard PPI in our analyses, as in previous studies in youth(65). Other methods of functional connectivity analyses may yield different findings. In addition, while other outcome measures could have been included, the PGBI-10M is the key LAMS-2 measure of behavioral and emotional dysregulation, and, as such, was the preferred outcome measure. Additionally, the contribution of pubertal development could not be considered as it was not measured during TIME1 assessments. Many of the LAMS youth were medicated, although no class of psychotropic medication was a non-zero predictor of future TIME2:PGBI-10M. Finally, there has been recent debate about inflation of predictions in neuroimaging studies in individuals with psychiatric disorders.(66) We used a well-validated approach that penalizes complex models using regularization, cross validation, and enforces sparsity in model fit. As in any study, magnitudes of parameter estimates that we observed for each predictor need to be examined and refined in future replications and meta-analyses.

This is the first study, to our knowledge, to use a multimodal neuroimaging approach to predict future behavioral and emotional dysregulation in youth. Specifically, we show that after accounting for prior severity of behavioral and emotional dysregulation, approximately one-third of the explained variance of the severity of these symptoms in the future was predicted by a combination of neuroimaging measures of reward circuitry function and white matter structure in tracts in the whole brain. This study demonstrates for the first time that neuroimaging measures reflecting underlying neuropathological processes are significant predictors of a substantial proportion of variance in future behavioral and emotional dysregulation in youth. This is an important step toward identifying neurobiological measures characterizing youth at greatest risk of poor outcome, and provides promising neural targets for future therapeutic interventions.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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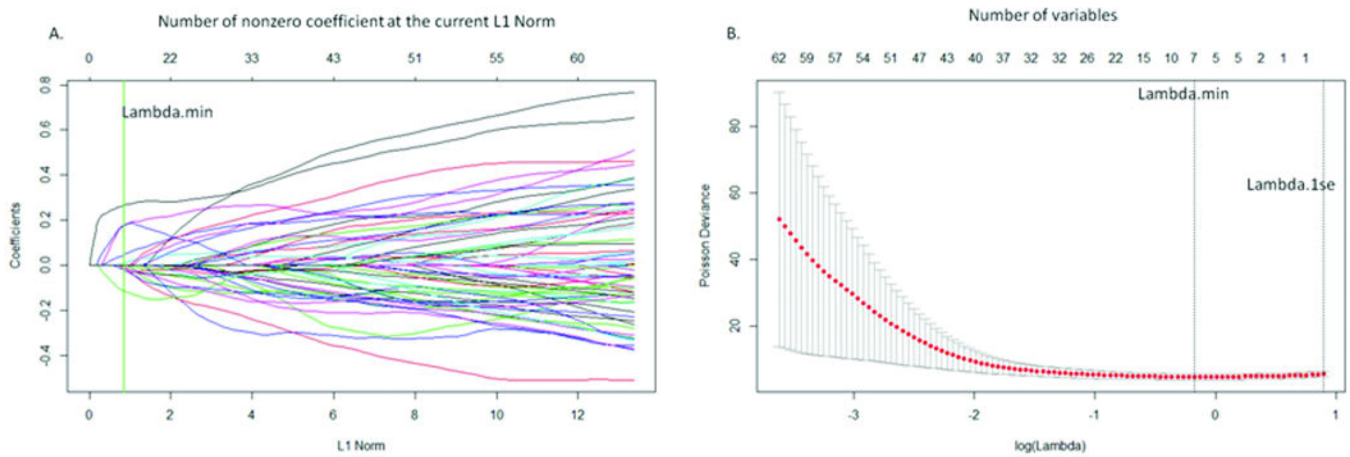

Figure 1. LASSO plots generated in GLMNET

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 λ varies. Lambda.min corresponds to the λ which minimizes mean squared error in the model and was used for the selection of the seven predictor variables B. Plot of non-zero variable fit after cross validation. Representation of the 10-fold cross validation performed in LASSO that chooses the optimal λ. Lambda.min corresponds to the λ which minimizes mean squared error and was used for variable selection. Lambda.1se corresponds to the λ that is one standard error from the lambda.min.

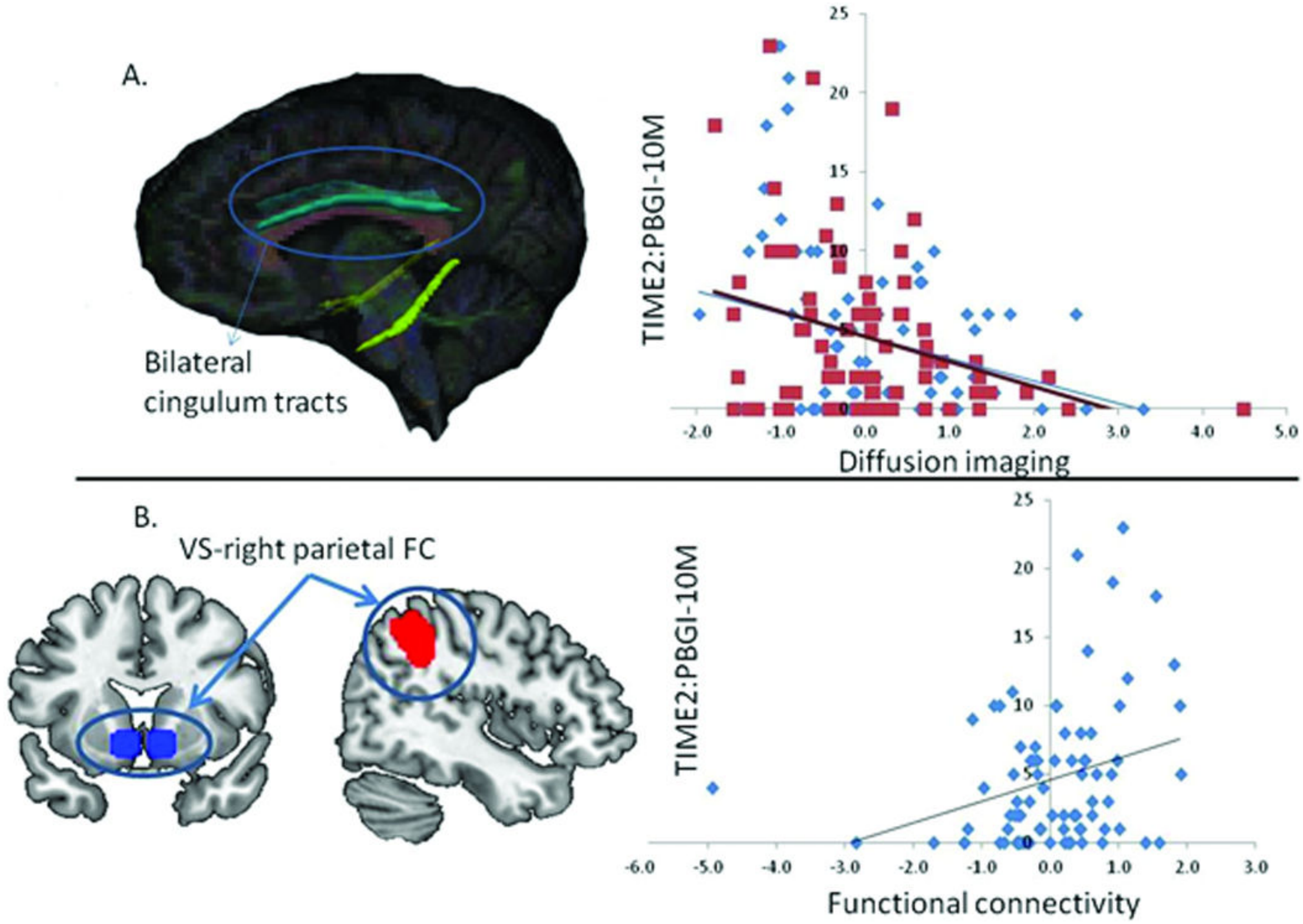

Figure 2. Representation of neural variables showing nonzero relationships with TIME2:PGBI-10M after LASSO regression and scatter plots of the linear relationships of these variables

All statistical analyses assumed an underlying Poisson distribution. A. Representation of bilateral cingulum tracts in a standard brain. Blue diamonds and trend line represent the relationship between left cingulum length and TIME2:PGBI-10M scores. Red squares and trend line represent the relationship between right cingulum length and TIME2:PGBI-10M scores. B. Representation of ventral striatum- right parietal functional connectivity (right parietal target region: mni: 48, −46, 52, k=314) in a standard brain. Scatter plot and trend line represent the relationship between vs-right parietal functional connectivity and TIME2:PGBI-10M scores.

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Table 1

Comparison of participants used in the analyses (n=80) and those who were removed due to movement, incomplete fMRI/DTI acquisition, or incomplete follow-up data (n=50).

	Participants included in data analysis n=80	Participants not included in data analysis n=50	Statistic	p
Demographic Information				
Age	14.0(2)	12.82(1.9)	$t_{(128)} = -3.32$	.001
Sex (females)	33	15	χ^2=1.67	.196
IQ	104.38(17.02)	94.46(13.22)	$t_{(121.9)} = -3.72$	<.001
SES (primary caregiver education)			χ^2= 9.54	.049
No/some HS	3	5		
HS Diploma	16	19		
Some post HS	19	10		
Associate's Degree	23	11		
Bachelor's Degree or higher	19	5		
Clinical Measures				
Semi-annual assessment closest to scan				
PGBIM10	6.04(5.95)	6.47(6.60)	$t_{(126)} = .38$	.705
Scan day assessments				
KDRS	4.13(4.8)	3.40(4.5)	$t_{(126)} = -.85$	.395
KMRS	4.60(7.0)	4.10(6.4)	$t_{(126)} = -.40$	.690
SCARED	10.63(10.2)	13.18(13.2)	$t_{(83.0)} = 1.16$	.251
Diagnosis				
Major Depressive Disorder	23	15	χ^2= .023	.879
Bipolar spectrum disorder	30	13	χ^2=1.84	.175
ADHD	61	43	χ^2= 1.84	.176
Anxiety Disorder	28	11	χ^2= 2.48	.116
Disruptive Behavior Disorder	47	38	χ^2=4.05	.044
Psychotropic medication use	48	27	χ^2= .45	.501
Site			χ^2=3.20	.202
University of Pittsburgh Medical Center	26	24		
Case Western Reserve University	21	11		
Cincinnati Children's Hospital	33	15		

Parental General Behavior Inventory-10 Item Mania scale (PGBI-10M), Screen for Child Anxiety Related Emotional Disorders(SCARED), Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale(KMRS), and Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale(KDRS). Data are mean (SD) for age, IQ, and clinical measures. For all other variables data are total n. P-values are = unless specified.

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Table 2

Reward-related neural activity and functional connectivity in LAMS youth at Time 1.

			MNI Coordinates				Statistic
Region	**BA**	**k**	**x**	**y**	**z**	**Test Statistic (df)**	$p_{uncorrected}$
Win>control Activity							
Right parietal cortex	40	399	48	−52	43	t(79)=6.24	<0.001
Left parietal cortex	40	443	−39	−58	46	t(79)=5.95	<0.001
Right prefrontal cortex	8	532	6	32	46	t(79)=6.00	<0.001
Corpus Callosum		125	6	−25	25	t(79)=5.46	<0.001
Right Insula		186	30	23	−5	t(79)=5.99	<0.001
Left motor cortex	6	372	−39	5	49	t(79)=5.60	<0.001
Right middle temporal gyrus	21	105	60	−31	−11	t(79)=5.03	<0.001
Right DLPFC	9	419	45	32	31	t(79)=4.89	<0.001
Left mPFC	10	234	−36	50	16	t(79)=5.34	<0.001
Left inferior frontal gyrus	45	180	−48	17	4	t(79)=5.03	<0.001
Right Primary visual area	17	39	12	−76	10	t(79)=3.93	<0.001
Left caudate		52	−9	8	4	t(79)=3.91	<0.001
Win>control Connectivity							
Right parietal cortex	40	314	48	−46	52	t(79)=4.59	<0.001
Left parietal cortex	7	365	−36	−52	55	t(79)=4.06	<0.001
Right middle frontal gyrus	9	289	42	38	22	t(79)=3.64	<0.001
Right prefrontal cortex	8	185	3	26	58	t(79)=3.17	<0.001

Win>Control Activity resulted from whole-brain analyses using voxelwise p<.001 and p<.05, 3DClusterSim corrected. Win>Control functional connectivity resulted from whole brain analyses using a bilateral ventral striatum seed region, voxelwise p<.05 and p<.05, 3DClusterSim corrected. Each row in the table represents the peak voxel within the specified region.

Abbreviations: BA = Brodmann area; df=degrees of freedom; k = cluster size in voxels; MNI=Montreal Neurological Institute coordinates; $p_{uncorrected}$=uncorrected voxelwise *p* value; t=t-test statistical value; DLPFC=dorsolateral prefrontal cortex.

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Table 3

Nonzero coefficients generated from GLMNET using a LASSO regression with Poisson family model.

Variable	LASSO derived Coefficient	Exponentiated coefficient	Percent deviance explained by the addition of variable to model
TIME1:PGBI-10M	0.255	1.29	.136
VS-right parietal functional connectivity	0.153	1.17	.082
Left cingulum length	−0.097	0.91	.061
Sex	0.146	1.16	.024
KMRS	0.034	1.03	.008
Right cingulum length	−0.008	0.99	.005
KDRS	0.001	1.00	.002

Exponentiated coefficient is the rate ratio change in the dependent variable (TIME2:PGBI-10M) corresponding to one unit change in the predictor variable.

Abbreviations: Time 1 Parental General Behavioral Inventory-10 Item mania scale (TIME1:PGBI-10M); Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS); Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale (KDRS). VS = Ventral Striatum