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Reward-related neural activity and structure predict future substance use in dysregulated youth

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Abstract

Background—Identifying youth who may engage in future substance use could facilitate early identification of substance use disorder vulnerability. We aimed to identify biomarkers that predicted future substance use in psychiatrically un-well youth.

Methods—LASSO regression for variable selection was used to predict substance use 24.3 months after neuroimaging assessment in 73 behaviorally and emotionally dysregulated youth

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aged 13.9 (sd=2.0), 30 female, from three clinical sites in the Longitudinal Assessment of Manic Symptoms (LAMS) study. Predictor variables included neural activity during a reward task, cortical thickness, clinical, and demographic variables.

Results—Future substance use was associated with higher left middle prefrontal cortex activity, lower left ventral anterior insula activity, thicker caudal anterior cingulate cortex, higher depression and lower mania scores, not using antipsychotic medication, more parental stress, older age. This combination of variables explained 60.4% of the variance in future substance use, and accurately classified 83.6%.

Conclusions—These variables explained a large portion of the variance, were useful classifiers of future substance use, and showed the value of combining multiple domains to provide a comprehensive understanding of substance use development. This may be a step toward identifying neural measures that can identify future substance use disorder risk, and act as targets for therapeutic interventions.

Keywords

substance use; prediction; GLMNET; fMRI; LASSO; youth

Introduction

Sensation seeking increases during adolescence (Kandel and Logan, 1984, Steinberg *et al.*, 2008) often at the expense of safer choices. Some risk-taking, for example, practicing difficult sporting maneuvers or applying to highly ranked schools or jobs, is beneficial to growth and survival. Other risks taken by youth, however, are associated with deleterious behaviors, such as substance use and substance use disorders. The propensity for risky behaviors, such as substance use, in youth may be related to reward circuitry development, specifically, reduced ventral striatal function and volume (Schneider *et al.*, 2012); and a delay in the development of prefrontal cortical regions implicated in cognitive control alongside the emergence of increased dopaminergic activity in subcortical regions during puberty (Steinberg *et al.*, 2008).

Reward circuitry comprises a widespread neural network, including ventral striatum, amygdala, and insula, and specific prefrontal cortical regions: ventrolateral prefrontal cortex (vlPFC;BA47), dorsal anterior cingulate (dACC; BA24/32), medial and middle prefrontal cortex (mPFCBA10). Reward circuitry related activity, along with sensation seeking personality traits and risk taking behaviors, characterized early onset drinking (Nees *et al.*, 2012). In addition, on a naturalistic risk taking task, activity in bilateral insula, parietal, orbitofrontal, and motor cortices, as well as left anterior cingulate cortex, together were able to discriminate between making a risky or safe choice on the next trial with 67% accuracy (Helfinstein *et al.*, 2014). Additionally, in adolescence, cortical maturation often corresponds with substance use onset (Shaw *et al.*, 2008). Animal studies reported differential changes in cortical thickness in adolescent animals exposed to substances (Vetreno *et al.*, 2016), while adolescent marijuana users showed reduced cortical thicknesses relative to non-users (Lopez-Larson *et al.*, 2011). The extent to which measures of reward circuitry function and structure in youth predict future substance use, however, remains to be determined.

Identifying in youth such predictors, alongside clinical and demographic predictors, would not only provide objective neural markers to identify risk of future substance use disorders, but would also provide targets to ultimately guide early intervention, treatment choice, and novel treatment developments.

Predicting clinical outcome from neuroimaging measures is a burgeoning field of research (Berkman and Falk, 2013). Measures of neural structure and function predicted response to psychotherapy, CBT, and psychotropic medications in adults and children with major depressive (MDD) and anxiety (AnxD) disorders (Forbes *et al.*, 2010, Fu *et al.*, 2013, Hum *et al.*, 2013, Masten *et al.*, 2011, McClure *et al.*, 2007, Morgan *et al.*, 2013, Pizzagalli, 2010, Shin *et al.*, 2013). Additionally, in youth, future positive mood and energy dysregulation was predicted by a combination of reward circuitry functional connectivity, white matter structure and clinical scores, together explaining 28% of the variance in clinical outcome (Bertocci *et al.*, 2016). The latter study in particular points to the feasibility of using a multimodal neuroimaging approach to identify markers of neural function that, in combination with clinical and demographic measures, can predict future behavioral outcomes in youth with psychiatric disorders. Large sample sizes, multimodal neuroimaging techniques, and statistical analyses that can evaluate large numbers of potential predictor variables are needed to fully examine the extent to which combinations of measures 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 (Kohannim *et al.*, 2012a, Kohannim *et al.*, 2012b, Luo *et al.*, 2015, Wang *et al.*, 2015, Zemmour *et al.*, 2015), and is gaining favor in clinical research (Bertocci *et al.*, 2016, Christensen *et al.*, 2014, Yan *et al.*, 2015). This technique evaluates a large number of potential predictor variables, relative to the number of study participants, while minimizing model error and minimizing the risk of overfitting through cross validation.

The goal of the present study was to identify measures of reward circuitry function and cortical structural thickness that predicted future substance use 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 (Findling *et al.*, 2010, Horwitz *et al.*, 2010). We hypothesized that in LAMS youth, future substance use would be predicted by increased prefrontal-cortical-striatal reward circuitry activity and reduced whole brain cortical thickness. We also aimed to determine the proportion of future substance use predicted by neuroimaging measures, and to test the discriminatory power of identified predictors.

Methods

Participants

One hundred and thirty youth, recruited from the LAMS1 cohort of 707 youth for whom parents were seeking psychiatric assessment and treatment participated in the neuroimaging component of LAMS2. All 130 youth from LAMS1 entered LAMS2 with a variety of symptoms and diagnoses. Inclusion criteria for the LAMS1 cohort were: no outpatient

treatment at a LAMS clinic in the last 12 months; 6-12 years of age; and without a sibling who was screened for LAMS1 (Findling *et al.*, 2010). Families of eligible children completed the Parental General Behavior Inventory–10 Item Mania scale (PGBI-10M). Children who scored ≥12 on this scale, and an age-sex-matched group of those who scored <12, were invited to participate in LAMS1. The 130 youth in the LAMS2 neuroimaging component were selected to include approximately equal numbers of youth: 1.with high (≥12) versus low (<12) PGBI-10M scores; 2.who were older (≥13 years) versus younger (≤12 years); 3.who were male versus female (each site was age and sex matched for each PGBI-10M subgroup).

Exclusion criteria for participating in the LAMS2 neuroimaging component included systemic medical illnesses, neurological disorders, history of trauma with loss of consciousness, use of non-psychotropic central nervous system effecting medications, IQ<70 assessed by the Wechsler Abbreviated Scale of Intelligence (WASI), positive drug and/or alcohol screen on scan day, significant visual disturbance, inability to communicate in English, autistic spectrum disorders/developmental delays, pregnancy, claustrophobia, and metal in the body.

Parents/guardians and youth provided written informed consent and assent, respectively, after receiving a complete study description.

The final sample included 73 LAMS youth (Age:*M*=13.91, *SD*=2.00, *Range*=9.89-17.71; 30 females; Table 1). 57 LAMS youth were excluded for behavioral data loss (n=5), excessive movement during neuroimaging acquisition (n=33), or cortical thickness processing problems (n=19; inability to read the pixelated data, mislabeled parcellations, non-symmetric colors, or missing cortical regions). Included youth were older, had higher IQ, and higher SES relative to excluded youth (Table 1).

Reward Task

Reward-related neural activity measures were acquired using a well-validated card guessing task with a reward component (Bebko *et al.*, 2014, Forbes *et al.*, 2009); supplemental materials).

Neuroimaging Data Analysis

fMRI data were collected on a 1) 3T Siemens Verio MRI scanner at Case Western Reserve University, 2) 3T Philips Achieva X-series MRI scanner at Cincinnati Children's Hospital, and 3) 3T Siemens Trio MRI scanner at University of Pittsburgh. We preprocessed and analyzed fMRI data using Statistical Parametric Mapping software (SPM8 http://www.fil.ion.ucl.ac.uk/spm). An axial 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (192 axial slices 1 mm thick; flip angle=9°; field of view=256×192 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 spatial smoothing using a Gaussian kernel (FWHM: 8mm). A two level random-effects procedure was used to conduct region of interest (ROI) analyses. At the first level we constructed whole brain statistical maps to evaluate the win>control and loss>control contrasts. Movement parameters obtained from the realignment stage of preprocessing served as covariates of no interest.

A single anatomically-defined, bilateral ROI mask containing reward-related regions (Caseras *et al.*, 2013, Nusslock *et al.*, 2012) from the WFU PickAtlas (Maldjian *et al.*, 2003) was used to avoid conducting multiple statistical tests over individual ROIs: dACC (BA24/32), mPFC (BA10), OFC (BA11), VLPFC (BA47), amygdala, insula, and VS (bilateral spheres centered on ±9, 9,-8; radius=8mm based on meta-analyses (Di Martino *et al.*, 2008, Postuma and Dagher, 2006)). Using a one-sample t-test, we extracted significant activity to win>control and loss>control (voxelwise $p<.001$, corrected with a 3D cluster forming threshold of $p<.05$ (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) over the entire ROI. Means of significant clusters were extracted using the MarsBaR (Brett *et al.*, 2002) toolbox in SPM.

Additionally, we examined gray matter structure across the whole brain as in other neuroimaging studies examining relationships between cortical thickness and risky behavior (Lopez-Larson *et al.*, 2011); supplemental materials). Structural thicknesses was calculated using the freely available Freesurfer (Fischl, 2012) software. An unbiased within-subject template space and image were created. Next, skull stripping, Talairach transformation and atlas registration were completed. Finally, generation of spherical surface maps and parcellations with common information from the within-subject template was performed. The quality of surface reconstruction and segmentation was visually assessed. Each structure was extracted and adjusted for individual mean whole-brain thickness.

Clinical Assessments

On or near scan day, parents/guardians completed the PGBI-10M to assess their child's behavioral and emotional dysregulation severity (Youngstrom *et al.*, 2005, Youngstrom *et al.*, 2008), and the Children's Affect Lability Scale (CALS) to assess their child's affective regulation (Gerson *et al.*, 1996). On scan day, parents and LAMS youth completed the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Mania Rating Scale (KMRS) (Axelson *et al.*, 2003) and Depression Rating Scale (KDRS) (Kaufman *et al.*, 1997) to assess hypo/mania and depressive symptom severity, respectively. LAMS youth also completed the Screen for Child Anxiety Related Emotional Disorders (SCARED) on scan day to assess anxiety symptoms over the last 6 months (Birmaher *et al.*, 1997).

Substance Use Measure

To assess substance use at scan day and post fMRI scan [mean follow-up days:741 (sd: 181.41)], questions concerning substance use from the KSADS (Kaufman *et al.*, 1997), the Child and Adolescent Symptom Inventory (CASI) (Lavigne *et al.*, 2009), and age appropriate versions of the Centers for Disease Control and Prevention's Youth Risk

Behavior Survey (YRBS) [Middle school:10-12 years of age; 2005 version; High school: 13-17 years of age; 2003 version; Adult:18-22 years of age; 2010 version] (www.cdc.gov/yrbs) were used. A report of substance use (*more* than a few sips of alcohol and/or any illicit drug use) on any of these measures put the participant into the substance user group.

Data Analytic Plan

The outcome measure used in this analysis was yes/no lifetime substance use. Of the 73 youth, 36 reported substance use 24 months post-scan. Clinical predictor variables on or near scan day included positive mood and energy dysregulation (PGBI-10M score), depressive symptoms, manic symptoms, anxious symptoms, and affective lability, diagnoses (ADHD, bipolar spectrum disorder, MDD, disruptive behavior disorder, and AnxD), medication status (taking versus not taking each psychotropic medication class: stimulant, non-stimulant ADHD, mood stabilizer, antipsychotic, and antidepressant medications). Demographic variables included age, IQ, and sex. Baseline measures of maternal education, parental life-stress (number of stressful events related to child's illness), and parental living arrangement (living with a new partner or alone) were also included as predictors (Kokkevi *et al.*, 2007a, Kokkevi *et al.*, 2007b). Neuroimaging predictor variables included the above BOLD measures to win>control and loss>control and the above whole brain gray matter cortical thickness variables. We additionally included scan site, and days between scan and follow up as predictor variables.

Given that our outcome variable was dichotomous and there were more predictor variables than observations, we used LASSO regression analysis with binomial family (logistic LASSO regression) for variable selection and reduction using the freely available GLMNET package in R (Friedman *et al.*, 2014). LASSO is a modified form of least squares regression that penalizes complex models with a regularization parameter (λ) (Tibshirani, 1996). This penalization method shrinks coefficients toward zero, and eliminates unimportant terms entirely (Friedman *et al.*, 2014, Friedman *et al.*, 2010, Tibshirani, 1996) thus minimizing prediction error, reducing the chances of overfitting through cross validation (CV), and enforcing sparsity (Tibshirani, 1996).

GLMNET approximates the loglikelihood and then uses coordinate descent algorithm (Revolutionary Analytics, 2013, Wu and Lange, 2008) computed along a regularization path (an inner weighted least squares loop) to optimize the penalized loglikelihood. Coefficients are stabilized by coordinate descent (optimization of each parameter separately, holding all others fixed). Regularization adds constraints to a problem to avoid over-fitting. Regularization in GLMNET for a binomial regression is performed by producing the path of tuning parameter (λ) along the range of included variables, thus identifying the optimal λ (http://web.stanford.edu/~hastie/glmnet/glmnet_alpha.html). GLMNET then uses CV to compute the mean CV error for each penalty term to guard against Type III errors (testing hypotheses suggested by the data). We used a k=10 fold CV approach.

A test statistic or p-value for LASSO that has a simple and exact asymptotic null distribution is still under development (Lockhart *et al.*, 2014). We thus provide three other measures that are meaningful for data inference: 1) rate ratio (exponentiated coefficients) of the nonzero coefficients identified in the LASSO model; 2) Cox & Snell R-square for variance in future

substance use explained by the model; 3) classification table results (cutoff =.1) from a hierarchical logistic regression analysis in SPSS, using the eight predictor variables identified from the LASSO model.

Post hoc sensitivity analysis

Of the 36 LAMS youth who at 24 months post-scan reported substance use, 15 also reported using substances at or prior to the scan. To test the importance of the combination of predictor variables derived from the LASSO, we examined the classification table from the logistic regression analysis after removing the 15 youth with substance use at scan. Additionally, to identify the nonzero variables related to *future* substance use only, we performed a new LASSO analysis, removing these 15 youth and including all of the original p=108 predictor variables.

Scan Site Signal Variability Reduction

We reduced signal variability between scan sites in two ways. First, we monitored signal-to-noise (SNR) monthly to ensure scanner stability over time with a Biomedical Informatics Research Network (fBIRN) phantom at each scan site (http://www.birncommunity.org). Second, we used scan site as a covariate in the LASSO models.

Results

Neuroimaging Results

LAMS youth showed significant activation to the win>control contrast in bilateral dACC (BA32) (MNI: -3,20, 46 and 3,20,46), left middle prefrontal cortex (mPFC; BA10) (MNI: -39,47,1 and -39,50,16), and bilateral ventral anterior insula MNI : 33,23,-5 and -48,17,1); and to the loss>control contrast, in bilateral dACC (BA32) (MNI: -9,8,52; 3,20,46; and 9,29,31) and ventral anterior insula (MNI: 30,20,-8 and -33,20,7) (voxelwise $p<.001$, clusterwise corrected $p<.05$, Table 2).

LASSO Results

Eight predictors together minimized mean squared error, enforced sparsity, (Friedman *et al.*, 2014) and optimized model fit (Figure 1 and supplement). These eight predictors and the direction of the relationships were as follows.

Substance use 24 months post-scan was predicted by greater left middle prefrontal cortical activity to win, lower left ventral anterior insula activity to loss, and thicker caudal anterior cingulate cortex. In addition, older youth, higher depression scores, lower mania (KMRS) scores, more parental stressful events and not being on an antipsychotic medication at scan predicted future substance use (Table 3).

The full model explained 60.4% of the variance in future substance use. Hierarchical logistic regression showed that left middle prefrontal cortical and left ventral anterior insula activity, together with left caudal anterior cingulate cortical thickness, explained 14.4% of future substance use variance over and above the clinical and demographic variables (45.7%; depression and mania scores, parental stress, age, and antipsychotic medication use).

Additionally, cutoff≤.1 from the logistic regression classification table correctly predicted 36/36 of future substance users and misidentified 12/37 of non-users as future substance users, correctly identifying 61/73 participants (83.6%).

Post hoc sensitivity analysis

After removing the 15 youth who reported substance use at scan, the model remained significant and the Cox & Snell R-square effect size increased from 0.6 to 0.63. The classification table using the eight non-zero predictor variables identified above (cutoff<.1) correctly predicted 21/21 future substance users and misidentified 6/37 non-users as future substance users (Cox & Snell=.631).

Additionally, in a new LASSO regression analysis including only the 58 youth who were not using substances at scan time, nonzero predictors of substance use were similar to the main analysis. Nonzero predictors were depression score, antipsychotic medication, parental stress at baseline, left middle prefrontal cortical activity to win, and right insula thickness. Notably absent variables in this post hoc LASSO analysis that may be driven by substance use prior to scan but were predictive of eventual use (see post hoc classification results above) included left caudal anterior cingulate thickness, left ventral anterior insula activity to loss, and mania scores.

Discussion

Our goal was to assess the ability of neuroimaging measures of reward circuitry activity and cortical thickness to predict future substance use in psychiatrically-unwell youth. We used LASSO regression, along with cross-validation, an approach that penalizes complex models with a regularization parameter and identifies the parameter that minimizes error, rendering unimportant coefficients as zero. Our LASSO analysis showed that engaging in substance use 24.3 months post-scan was predicted by a combination of neural activity to win and loss, cortical structure, and clinical and demographic characteristics. These findings explained 60.4% of the variance in substance use 24.3 months after neuroimaging assessment. Furthermore, neuroimaging measures incrementally predicted 14.7% of the variance, i.e., approximately a quarter of the explained variance, in this outcome measure. All eight predictor measures correctly classified 100% of youth who would use substances 24 months later, while misidentifying only 32% of non-users as future users. Including all identified nonzero variables in a logistic regression analysis, both with and without the 15 current users, successfully identified all future substance users 24 months post-scan.

In humans, the middle prefrontal cortex has been shown to be activated both by cognitively demanding tasks, e.g., working memory, and reward, and may subserve the higher cognitive aspects of reward value processing and related, goal-directed behaviors (Pochon *et al.*, 2002). Our present finding of elevated left middle prefrontal cortical activity to reward in youth may thus reflect undue attention to, and higher order processing of, reward obtained during the task, which, in turn, may predispose to risk-taking behaviors, such as substance use. The left lateralization of our finding may reflect the role of the left hemisphere in approach related behaviors (Davidson, 1992, Davidson *et al.*, 1990)(Figure 2).

We showed that lower ventral anterior left insula activity to loss>control predicted more substance use in the future, although this was no longer the case after excluding the 15 youth who were using substances at scan. Subdivisions of the insula have been shown to have distinct patterns of functional connectivity (Deen *et al.*, 2011). The ventral anterior insula is functionally connected to the anterior cingulate cortex and may have role in the processing of emotion (Deen *et al.*, 2011). Our finding that lower left ventral anterior insula activity to loss predicted future substance use may thus suggest that reduced perception of emotion during loss may have a role in the development of risky behavior in youth. In support of this, in abstinent drug users, insula activity was reported during decision-making (Stewart *et al.*, 2014a, Stewart *et al.*, 2014b), while attenuation of bilateral insula activity was shown to predict relapse after one year among abstinent methamphetamine dependent youth (Gowin *et al.*, 2014). Furthermore, individuals with insula lesions placed higher bets and showed less sensitivity to odds compared with controls (Clark *et al.*, 2008). In healthy individuals, however, greater insula activity was associated with the safer choice during performance of a risky stock market decision-making paradigm (Kuhnen and Knutson, 2005). The above findings, taken together with our finding that lower left ventral anterior insula activity to loss may have been associated with substance use at scan, may thus suggest that LAMS youth who engaged in substance use may have perceived less emotion and, as a result, may have been less sensitive to the risks involved, and consequent losses sustained, when making decisions during the card number guessing task.

We also showed that greater right insula thickness predicted future substance use in the 58 youth who were not using substances at scan. Animal studies suggest normative thinning of subcortical and cingulate regions with age (Vetreno *et al.*, 2016). Furthermore, the right insula is implicated in conscious awareness of interoception (Naqvi and Bechara, 2009). Our finding regarding right insula thickness may thus suggest that abnormal neurodevelopment of this region (ie., reduced pruning) may predispose to abnormally heightened awareness of interoceptive processes that, in turn, may have a deleterious impact on decision-making, but this needs further study.

Other studies have shown that neuroimaging measures may predict future substance use (Becker et al., 2015), although, in contrast to our findings, a previous report indicated that measures of neural activity may be less important predictors of risky behaviors than other factors in youth. This study reported that a factor consisting of insula, putamen, caudate nucleus, amygdala, cerebellar vermis, and prefrontal cortex activity, when combined with a personality factor and a genetic factor, was the least important factor in predicting drinking in adolescence (Heinrich *et al.*, 2016). The fact that a significant proportion of the variance in future substance use was predicted by neuroimaging measures in our study, however, highlights a need for future studies to further examine the role of neuroimaging measures as predictors of risky behaviors in youth.

We additionally showed that greater cortical thickness in the caudal anterior cingulate cortex predicted future substance use, but not after excluding the 15 youth who used substances at scan. In young adults, left caudal anterior cingulate cortex was thicker in binge drinkers relative to light drinkers (Mashhoon *et al.*, 2014). Additionally, normative cingulate cortical thinning was not observed in animals exposed to ethanol (Vetreno *et al.*, 2016). Thus, similar

to the left insula activity to loss finding above, greater anterior cingulate cortical thickness may be a marker of current substance use. More studies are needed to better understand this structural finding.

Non-neuroimaging variables also predicted future substance use. Consistent with the literature, older participants (Grant and Dawson, 1997, Kandel and Logan, 1984) and youth with higher depression scores (Deykin *et al.*, 1987, Grigsby *et al.*, 2016) more often reported future substance use. Youth not prescribed an antipsychotic medication at time of neuroimaging assessment were also more likely to use substances in the future, likely reflecting the moderating effect of these medications on psychotic and risk-taking behaviors. Intriguingly, youth with lower mania scores were also more likely to report future substance use. This may reflect the fact that youth with lower mania scores were less likely to be taking antipsychotic medication (p=.006), and thus did not benefit from the moderating effect of antipsychotic medications behaviors. While we do not suggest that youth be prescribed antipsychotic medication as a measure to reduce risk of future substance use, our findings do suggest that common patterns of neural activity may be associated with psychotic symptoms and substance use. This warrants further study. Finally, increased parental stress due to child's illness, predicted future substance use in youth. This accords with research showing that parental psychological distress is associated with emotional and conduct problems in children (Amrock and Weitzman, 2014, Reeb *et al.*, 2015). Our findings thus add to present understanding of the role that parental stress and related behaviors may have on child behavior long-term, and suggest that these factors may be used to identify those high risk families most in need of intervention.

Limitations of the present study included the inability to assess the contribution of pubertal development and other psychosocial factors that show associations with substance use, such as sibling and peer substance use and parental monitoring (Kokkevi *et al.*, 2007a, Kokkevi *et al.*, 2007b), as they were not measured at scan time. Although the age of greatest risk for substance use was not yet reached by some youth in our sample, a larger portion of the LAMS sample report substance use than is expected from the general population (Abuse, 2014). As the children in the LAMS sample are, and have been, behaviorally and emotionally dysregulated for at least five years and for as many as ten years, and are at risk for a myriad of psychiatric disorders, it is, perhaps not unexpected that they engage in substance use at a higher rate than we see in healthy children. Finally, this analysis was designed post hoc and we therefore were not able to control for substance use at the initial scan visit. Additionally we suspect that some of the misidentification as a substance user may, in fact, be due to the subjective account of substance use by participants. Although the statistical methods utilized here (LASSO with cross-validation) do well at identifying predictors, the estimates may shrink, and error rates for classification of users may be higher, in new, independent samples.

We believe this is the first study to use functional and structural neuroimaging measures to predict future substance use in youth. Specifically, we show that approximately a quarter of the explained variance in future substance use was predicted by neuroimaging measures, especially measures of reward circuitry function. Furthermore, the high discriminative ability to identify future substance use in youth highlights the utility of using a combination

of neuroimaging, clinical and demographic measures to help identify those youth most at risk of future substance use. This is an important step toward identifying neurobiological measures characterizing youth at risk of substance use, and provides promising neural targets for the development of novel future therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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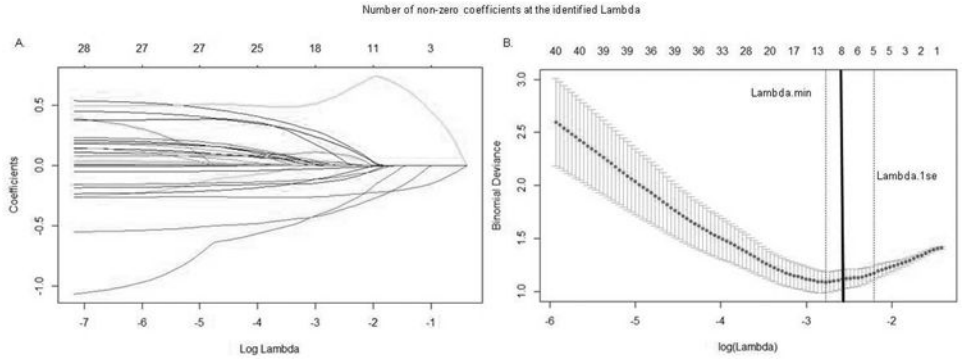

Figure 1. LASSO plots generated in GLMNET

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. B. Plot of non-zero variable fit after cross validation. Representation of the 10-fold cross validation performed in GLMNET using LASSO which evaluates the error associated with each lambda. Lambda.min corresponds to the λ which minimizes mean squared error. Lambda.1se corresponds to the λ that is one standard error from the lambda.min. Solid black line corresponds to the optimal lambda selected due to significantly improved model fit over the Lambda.min and Lamba.1se based on chi square residual deviance comparisons (supplemental).

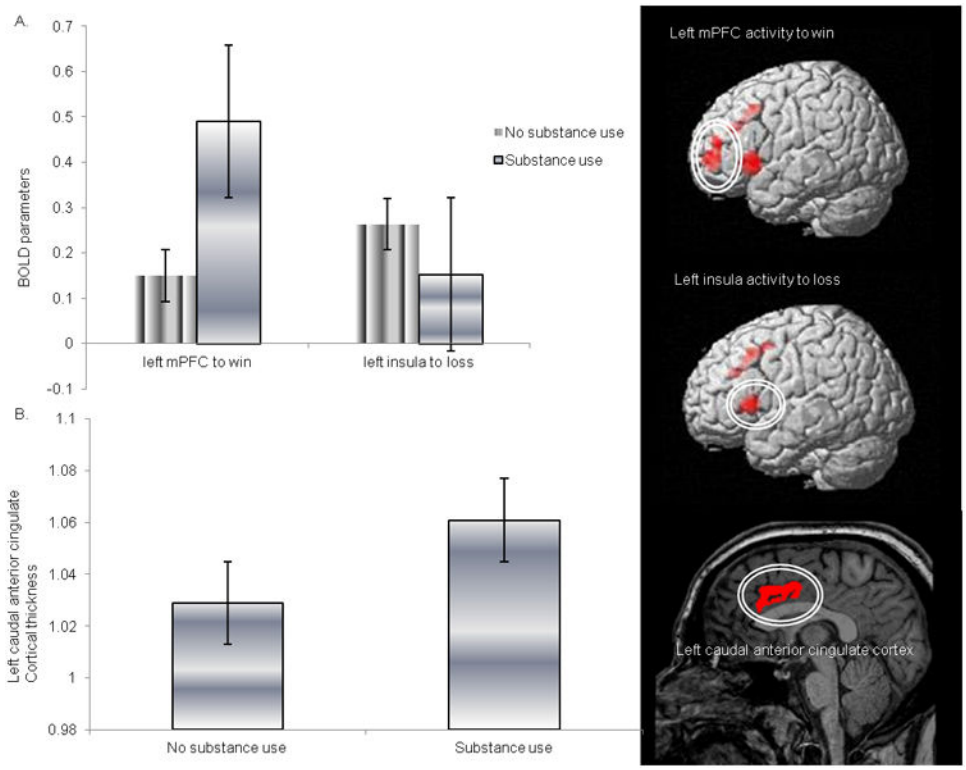

Figure 2. Comparisons of neural measures of substance users and non-users 24.3 months post-scan and representation of the region on an average brain image

A. Reward-related left mPFC and left ventral anterior insula activity. B. Left caudal anterior cingulate thickness between the two groups (representative image). Thickness variables were adjusted for individual mean cortical thickness. Bars represent the standard error.

Table 1

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

	Total LAMS Imaging Sample n=130 M(SD/Range) or Proportion	Included Participants n=73 M(SD) or Proportion	Excluded Participants n=57 M(SD/Range) or Proportion	Statistic Comparing Included vs Excluded Participants	
Demographic Information					*p* value
Age (years)	13.54(2.04/9.89-17.71)	13.92(2.0)	13.06(2.0)	t_{128}=-2.4	.018*
IQ	100.56(16.35/70-140)	105.44(17.3)	94.32(12.7)	$t_{127.6}$=-4.23	<0.001*
SES (maternal education)				χ^2=12.86	<0.001*
No/some HS	8/130	0/73	8/57		
GED or HS Diploma	35/130	15/73	20/57		
Some post HS	29/130	19/73	10/57		
Associate's Degree	34/130	21/73	13/57		
Bachelor's Degree or higher	24/130	18/73	6/57		
Sex (females)	48/130	30/73	18/57	χ^2=0.87	.351
Clinical Measures					
CALS	18.09(13.77/0-62)	17.30(13.0)	19.15(14.8)	t_{126}=0.75	.456
PGBI-10M	6.15(6.17/ 0-24)	5.96(6.0)	6.39(6.4)	t_{127}=0.39	.695
KDRS	3.85(4.68/0-24)	4.16(4.9)	3.44(4.4)	t_{126}=-0.87	.385
KMRS	4.41(6.77/0-31)	4.44(6.9)	4.38(6.7)	t_{126}=0.05	.963
SCARED	11.64(11.47/0-53)	10.93(10.8)	12.59(12.4)	t_{125}=0.81	.422
Current Medication Use					
Antidepressant	20/130	11/73	9/57	χ^2=0.00	1.0
Antipsychotic	27/130	20/73	7/57	χ^2=3.57	.059
Mood	11/130	8/73	3/57	χ^2=0.71	.401
Stabilizer					
Non-stimulant	11/130	6/73	5/57	χ^2=.00	1.0
Stimulant	49/130	29/73	20/57	χ^2=0.13	.720

Abbreviations: *=significant at p<05; CALS=Child Affect Lability Scale (parent rating); GED=general education development test; HS=high school; IQ=intelligence quotient Wechsler Intelligence test; KDRS=Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present Episode Depression Rating Scale; KMRS=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; Statistical comparisons between included and excluded participants, t=t-statistic value; χ^2=chi-squared statistic value.

Table 2

Reward-related activity in 73 LAMS youth.

Contrast				MNI Coordinates			Statistic	
Region	**BA**	**side**	**k**	**x**	**y**	**z**	**Test Statistic(*df*)**	***p***
Win>control activity								
dACC	32	L	17	-3	20	46	$t_{(72)}$=6.49	0.001
dACC	32	R	40	3	20	46	$t_{(72)}$ = 6.31	0.001
insula		R	105	33	23	-5	$t_{(72)}$ = 5.61	0.001
insula		L	80	-48	17	1	$t_{(72)}$=4.70	0.001
mPFC	10	L	25	-39	47	1	$t_{(72)}$ = 5.60	0.001
mPFC	10	L	11	-39	50	16	$t_{(72)}$ = 5.34	0.001
Loss>control								
dACC activity	32	L	27	-9	8	52	$t_{(72)}$ = 5.53	0.001
dACC	32	R	25	3	20	46	$t_{(72)}$ = 5.42	0.001
dACC	32	R	11	9	29	31	$t_{(72)}$=4.64	0.001
insula		R	39	30	20	-8	$t_{(72)}$=4.54	0.001
insula		L	40	-33	20	7	$t_{(72)}$=4.06	0.001

Region of interest analyses using voxelwise $p<0.001$ and cluster corrected $p<0.05$. Table rows represent the peak voxel within the specified region. Abbreviations: BA=Brodmann area; dACC=dorsal anterior cingulate cortex; *df*=degrees of freedom; k=cluster size in voxels; MNI=Montreal Neurological Institute coordinates; mPFC= middle prefrontal cortex; *p*=uncorrected voxelwise probability value; *t*=t-test statistical value; vlPFC=ventrolateral prefrontal cortex.

Table 3

Nonzero coefficients generated from GLMNET using a LASSO regression with binomial family model. Exponentiated coefficient is the rate ratio change in the dependent variable (future substance use) corresponding to one unit change in the predictor variable.

Variable	LASSO derived Exponentiated coefficient
Antipsychotic medication	.35
Age	1.20
Depression scale	1.07
Left middle prefrontal cortex to win>control	1.75
Parental stress at baseline	1.05
Mania scale	.98
Left ventral anterior insula activity to loss>control	0.83
Left caudal anterior cingulate thickness	1.39