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Clinical, cortical thickness and neural activity predictors of future affective lability in youth at risk for bipolar disorder: initial discovery and independent sample replication

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Abstract

We aimed to identify markers of future affective lability in youth at bipolar disorder risk from the Pittsburgh Bipolar Offspring Study (BIOS) (n=41, age=14, SD=2.30), and validate these predictors in an independent sample from the Longitudinal Assessment of Manic Symptoms study (LAMS) (n=55, age=13.7, SD=1.9). We included factors of *mixed/mania*, *irritability*, and *anxiety/depression* (29 months post MRI scan) in regularized regression models. Clinical and demographic variables, along with neural activity during reward and emotion processing and gray matter structure in all cortical regions at baseline, were used to predict future affective lability factor scores, using regularized regression. Future affective lability factor scores were predicted in both samples by unique combinations of baseline neural structure, function, and clinical characteristics.

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Supplementary information is available at MP's website

Lower bilateral parietal cortical thickness, greater left ventrolateral prefrontal cortex thickness, lower right transverse temporal cortex thickness, greater self-reported depression, mania severity, and age at scan predicted greater future *mixed/mania* factor score. Lower bilateral parietal cortical thickness, greater right entorhinal cortical thickness, greater right fusiform gyral activity during emotional face processing, diagnosis of Major Depressive Disorder, and greater self-reported depression severity predicted greater *irritability* factor score. Greater self-reported depression severity predicted greater *anxiety/depression* factor score. Elucidating unique clinical and neural predictors of future specific affective lability factors is a step toward identifying objective markers of bipolar disorder risk, to provide neural targets to better guide and monitor early interventions in bipolar disorder at-risk youth.

Keywords

youth; affective lability; prediction; MRI; cortical thickness

Introduction

Bipolar disorder (BD) is a major psychiatric illness that is challenging to diagnose, especially in pediatric samples, due to similarities of symptoms with other disorders, and challenges with consistency of parent and self-reports. The incidence of BD is 1–3% of the population and, currently, risk for the development of BD is best predicted by genetics, with heritability rates from 59–87% [1,2]. The absence of objective markers that are predictive of psychiatric outcomes hinders improvement in risk identification and the development of new, pathophysiologically-based interventions for BD.

Affective lability, a sudden, exaggerated, unpredictable, and developmentally inappropriate change in emotion, is a key prodromal feature of BD[3–8], and is present in adults with BD even when euthymic [9]. Identified within the self-reported measures of affective lability for youth and adults are three specific factors: *mixed/mania*, *irritability*, and *anxiety/depression* [4,10]. Youth with BD reported higher *mania*, *irritability*, and *anxiety/depression* factor scores than youth without BD [4]. While high scores on some of these factors are also present to a greater or lesser extent in other disorders in youth [11,12], these affective lability factors are noted prodromal features of BD in youth, [5,13–15] and point to underlying mechanisms of BD. Identifying neural predictors of future high scores on these affective lability factors in youth is thus a promising way forward to provide objective biological markers of future BD risk before diagnosable symptoms emerge, and can provide neural targets to guide and monitor interventions to delay or even prevent future mental health problems in BD-at-risk youth.

While there is a growing body of neuroimaging studies showing that aberrant prefrontal activity and connectivity are related to the development of BD, especially during emotion processing and regulation tasks[16–18], the neural basis of affective lability in general, and of its specific factors, is largely unknown. A recent study examining the neurocognitive correlates of affective lability in adults showed that current affective lability was related to deficits in executive functioning, presumed to involve prefrontal cortical areas [19]. In parallel,

lower prefrontal cortical thickness [20,21] and larger subcortical volumes [22], especially in the amygdala[22], are evident in individuals with BD relative to healthy individuals, along with higher prefrontal cortical thickness in at-risk populations relative to healthy [21]; and there is a large literature showing lower prefrontal cortical activity and elevated amygdala activity during a variety of emotion processing and emotional regulation tasks in youth and adults with BD[1]. Together, these patterns of aberrant prefrontal-amygdala structure, activity, and connectivity may underlie affective lability. Nonetheless, the extent to which aberrant prefrontal cortical-amygdala structure and function predict *future* affective lability remains unknown.

We recruited youth from the Bipolar Offspring Study (BIOS), an ongoing longitudinal study of youth across a range of genetic risk for BD [23–25]. We hypothesized that future affective lability factor scores of *mixed/mania*, *irritability*, and *anxiety/depression*, derived from affective lability scales [4,10], would be predicted by: 1) neural function, measured by the magnitude of whole brain reward and emotion processing circuitry(Figure 1); and 2) gray matter structure in regions supporting reward and emotion processing. We specifically hypothesized that lower prefrontal cortical thickness and activity and higher amygdala activity would predict greater future affective lability. The absence of previous neuroimaging studies of affective lability did not allow us to make specific hypotheses regarding relationships between neuroimaging measures and severity of specific affective lability factors. We also aimed to determine the relative proportion of future affective lability predicted by neural measures, over and above clinical and demographic measures. Finally, we aimed to replicate findings from the BIOS sample in an independent sample of youth from the Longitudinal Assessment of Manic Symptoms (LAMS) study.

Methods

Participants

Participants in the main analysis comprised BIOS youth with two levels of genetic risk for BD development: 1. Offspring with a parent with BD (Offspring of Bipolar Parents, OBP, n=20, age=14.1(2.39)), with higher than normal risk for BD[26]; and 2. Offspring with a parent with a non-BD Axis-1 disorder (Offspring of Community Psychiatric Control Parents, OCP, n=21, age=13.9(2.28)), who have lower risk for BD than OBP[23,24], but potentially higher risk [24,27] than the healthy population [24,27]. The participants in the validation study (n=55, mean age=13.7(1.9)) were youth with a variety of psychiatric disorders presenting with behavioral and emotional dysregulation recruited from the Longitudinal Assessment of Mania Symptoms (LAMS) study, previously described in detail [16,28,29], and in the supplementary information (SI) (Table 1). LAMS youth had more severe mania scores, were more likely to have a lifetime diagnosis of Major Depressive Disorder, and had fewer days between scan and follow-up than BIOS youth (Table 1). Institutional Review Boards approved both studies. Parent/guardian consent and child assent were obtained.

Clinical Assessments

BIOS Youth—Child self-reports on the scan day included the Child Affective Lability Scale (CALS) [30]; the Screen for Child Anxiety Related Emotional Disorders (SCARED)[31];

and the Mood and Feelings Questionnaire (MFQ), a validated measure of depressive symptoms [32]. Parent report of the CALS on scan day was also obtained. Assessments near the scan day (mean time between assessment and scan day=72.8 days) included the Depression Rating Scale (KDRS)[33] and Mania Rating Scale (KMRS) [34] supplements from the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version, with questions from Washington University (K-SADS-PL-W), a well-validated clinician interview with good psychometric properties [33]. Psychiatric diagnoses were confirmed by a licensed psychiatrist or psychologist, and included major depressive disorder (MDD), Anxiety disorder (AnxD), and ADHD.

Affective lability measures were also obtained at follow-up interviews (TIME2) [(mean=29.6 months (range:12.2–52.4 months)] after neuroimaging scans. Owing to some participants aging into adulthood, both CALS and Affective Lability Scale (ALS)[10] measures were used at TIME2, hereafter: TIME2:ALS. Factors for the CALS and the ALS were previously identified [4,10], and included: *irritability*, *mixed/mania*, and *depression/anxiety*. We calculated the mean question score across all questions for each factor (*mixed/mania, irritability*, and *anxiety/depression*); and used these as outcome measures (SI).

See SI for the following information: task descriptions, neuroimaging data acquisition, preprocessing, and first-level processing. LAMS clinical assessments, exclusion criteria, and proportion of LAMS youth with a parent with BD.

Data Analysis

Mean factor score of TIME2:ALS *mixed/mania*, *irritability*, and *anxiety/depression* factors were dependent variables in three separate regularized regression analyses. The square root transformation was used, to adjust positively skewed data. Given that we had wide data and correlated predictor variables (r>.6), we used regularized regression with an elastic net for data selection and reduction using the GLMNET package in R[35]. This machine learning regularization method shrinks coefficients toward zero and eliminates unimportant terms entirely [35–37], minimizing prediction error, reducing the chances of overfitting, and enforcing sparsity in the solution. (SI)

TIME1 predictor variables acquired on or near scan-day included BOLD and cortical thickness neuroimaging measures (Table 2 and SI); TIME1:CALS mean factor scores:TIME1:*mixed/mania*, TIME1:*irritability*, and TIME1:*anxiety/depression*; TIME1:KMRS, TIME1:KDRS, TIME1:SCARED, TIME1:MFQ scores and diagnoses (TIME1:ADHD, TIME1:MDD, TIME1:AnxD); TIME1:age; TIME1:IQ; TIME1:sex; TIME1:medication status (taking versus not taking psychotropic medication); group (OBP, OCP); maternal education; handedness; and days between MRI scan-TIME2:ALS factors. Subsequently, using linear regression, we calculated the significance of, and r2 values associated with, each model.

Independent sample validation analysis: the models identified above in BIOS youth were tested using an independent group of high-risk youth from the LAMS study. We used a two-step procedure to test the utility of these findings in this independent sample.

1. We used the identified non-zero variables from BIOS youth in standard linear regression analyses. We reported the significance of the models, r2, and beta coefficients to show directions of relationships.

2. Given that the LAMS sample comprised youth with higher levels of psychopathology than BIOS youth, we compared LAMS youth with high and low parent-reported CALS at TIME1 (normative cutoff score=9[30]).

Results

BIOS participants

Greater mean score for the *mixed/mania* factor was predicted by greater cortical thickness in left pars orbitalis (coefficient=0.399) and pars triangularis of the inferior frontal gyrus (coefficient=0.455) [hereafter: left ventrolateral prefrontal cortex (vlPFC)]; lower thickness of the left precuneus (coefficient=−0.677) and right supramarginal gyrus (coefficient=−0.222); lower thickness of the right transverse temporal cortex (TTC;coefficient=−0.070); greater age (coefficient=.0002); greater TIME1:*mixed/mania* factor score (coefficient=0.070); and greater TIME1:MFQ (coefficient=0.005) self-report (Table 3A). These eight non-zero variables explained 67.2% of the variance in the mean score for the *mixed/mania* factor. Clinical variables explained 41.5%, and neuroimaging variables added 25.6%.

Greater mean score for the *irritability* factor was predicted by greater right fusiform gyral activity during emotional face processing (coefficient=0.001); greater right entorhinal cortical thickness (coefficient=0.213); lower left precuneus cortical thickness (coefficient=−0.239); greater TIME1:MFQ score (coefficient=0.007); and MDD diagnosis at TIME1 (coefficient=0.016) (Table 3B). These non-zero variables explained 62.5% of the variance in the mean score for the *irritability* factor. Clinical variables explained 46.9%, and neuroimaging variables added 15.7%.

Greater mean score for the *anxiety/depression* factor was predicted by greater self-reported TIME1:MFQ score (coefficient=0.004), which predicted 28.7% of the variance (Table 3C).

Independent LAMS sample validation

1. (Table 3 for beta coefficients; SI for ANOVA tables). For the *mixed/mania* factor, the eight non-zero variables above in BIOS youth identified a significant model in the LAMS sample (F(8,45)=3.71, p=.002), and explained 39.8% of the variance. Clinical variables and age explained 31.5%, and neuroimaging variables added 8.3%, in this independent sample. For the *irritability* factor, the five non-zero variables above in BIOS youth identified a significant model in the LAMS sample (F(5,48)=4.61, p=.002), and explained 32.4% of the variance. Clinical variables explained 21.1%, and neuroimaging variables added 11.3%. The depression severity variable explained 11.8% of the *anxiety/depression* factor mean score (F(1,52)=6.97, p=.011).

The directions of the majority of the beta coefficients for the predictors of the three factors in the BIOS and the LAMS samples were consistent (Table 3). For the future *mixed/mania*

factor, directions of predictive effects were consistent in both BIOS and LAMS youth for: TIME1:*mixed/mania* factor score, TIME1:MFQ score, and left pars triangularis, right supramarginal, and right TTC thickness. For the future *irritability* factor, directions of predictive effects were consistent in both samples for: TIME1:MFQ score, right fusiform gyral activity, and right entorhinal cortical thickness. For the future *anxiety/depression* factor, directions of predictive effects were consistent for TIME1:MFQ score. Opposite directions of predictive relationships in LAMS and BIOS youth were shown for the following relationships and were not the result of multicollinearity (all tolerance >.728): left pars orbitalis thickness-*mixed/mania* factor score, left precuneus thickness-*mixed/mania* and -*irritability* factor scores, MDD diagnosis-*irritability* factor score, and, weakly, for age-*mixed/mania* factor score (Table 3).

2. Less than 1/3 (18/55) of the LAMS youth had TIME1:CALS-P scores below the cutoff score=9 (mean=4.78 SD=3.14), similar to TIME1:CALS-P scores for all BIOS youth (mean=5.45 SD=7.79; t(56)=.352, p=.726). Only 6/41 (15%) of BIOS youth had a TIME1:CALS-P score above the cutoff score=9. LAMS youth with lower TIME1:CALS-P scores showed directions of predictor-factor score relationships consistent with those of BIOS youth for: 1.left pars orbitalis thickness-*mixed/mania* factor score; 2.age-*mixed/mania* factor score, 3.MDD diagnosis-*irritability* factor score (Table 3). LAMS youth with higher TIME1:CALS-P scores (cutoff>9, n=39, mean=22.27 SD=1.97) showed opposite directions of relationships to those of BIOS youth, except for the relationship between age and *mixed/mania* factor score. Here, positive relationships were observed between these measures in both LAMS subgroups (Table 3).

To determine whether the different relationships in high- and low-scoring TIME1:CALS-P LAMS youth were due to differences in left pars orbitalis cortical thickness, age and MDD diagnosis, the magnitudes of these predictors were compared between LAMS TIME1:CALS-P subgroups. None differed significantly between LAMS subgroups (Figure 2B).

Left precuneus thickness was negatively related to both future *mixed/mania* and *irritability* factor scores in BIOS youth, but these relationships were positive for all LAMS youth and for both TIME1:CALS-P subgroups (Table 3). There were no differences in left precuneus cortical thickness between LAMS TIME1:CALS-P subgroups (Figure 2B).

Discussion

In youth at risk for BD, scores on affective lability factors two years after an MRI scan (mean 29 and 24.8 months) in two independent youth samples were predicted by unique combinations of clinical and neural measures at scan, despite differing processing methods. These findings indicate neural markers of specific prodromal features of BD and can help elucidate underlying neural mechanisms predisposing to BD in youth.

In BIOS youth, future *mixed/mania* and future *irritability* factor scores were predicted by lower parietal cortical thickness. This parallels findings of lower parietal cortical thickness in adults with BD, BD at-risk youth and adults, and depressed youth relative to healthy

adults and youth [20,38–42]. The fronto-partietal-cingulo network is implicated in phonological decision making [43] and executive functioning [44,45], and functional dysregulation in this network is associated with psychopathology [16,17]. Thus, lower parietal cortical thickness may lead to lower executive functioning and emotional regulation capacity and predispose to higher future mixed/mania and irritability.

Greater left vlPFC cortical thickness predicted greater future *mixed/mania* factor score in BIOS youth. Greater left prefrontal cortical thickness was reported in BD relative to healthy adults[46,47]. Additionally, longitudinal increases in thickness of the left inferior frontal gyrus, which includes the left vlPFC, were reported in at-risk young adults who later developed MDD, potentially the result of insufficient synaptic pruning, although change in cortical thickness was unrelated to depression severity[48]. Furthermore, abnormally elevated left vlPFC activity during uncertain reward expectancy was reported in adults with BD across different mood episodes [49,50]. Abnormally increased cortical thickness in the left vlPFC may thus predispose to risk for future BD and mood disorders in general, and abnormally elevated reward sensitivity, a characteristic of BD [1,49–51].

Lower right TTC cortical thickness [52] predicted greater future *mixed/mania* factor score in BIOS youth, paralleling findings of lower cortical thickness in this region in pediatric-onset depression [39]. The right TTC is involved in social processing, specifically eye gaze interpretation and attribution [53], and auditory processing [54]. Lower right TTC cortical thickness may thus predispose to abnormalities interpreting emotional cues, and to a range of disorders characterized by these abnormalities, including BD, MDD, autism spectrum disorders, and schizophrenia[55–58]. The combination of the above cortical thickness measures may result in difficulty regulating sensory social processing, behaviors, and emotions in rewarding contexts, and thereby predispose to hypo/mania in at-risk youth. Importantly, all the above neural measures, together with TIME1 affective lability and TIME1 depression severity, explained 67.2% of the variance in the *mixed/mania* factor, with neuroimaging variables contributing over one-fourth of the explained variance.

Predictors of greater future *irritability* factor score explained 62.5% of the variance, nearly one-fourth of which were explained by neuroimaging variables, and included, along with lower parietal thickness discussed above, greater depression severity and MDD diagnosis, greater right fusiform activity during emotion processing, and greater right entorhinal cortical thickness. The fusiform gyrus, especially right fusiform gyrus [59], supports face processing, social communication [60], and facial identity processing [61]. Normative decreases in right fusiform activity to emotional faces with age are absent in youth high in irritability[62], and may reflect an abnormal perception of facial stimuli as potentially threatening. The association of greater right fusiform gyral activity to emotional faces and greater future irritability may reflect this abnormal process. The entorhinal cortex is a key component of the medial temporal lobe episodic memory network [63]. This region also has connections with cortical regions implicated in emotion and reward processing [64], and encodes motivational aspects of memory [65]. Greater entorhinal cortical thickness may thus predispose to enhanced encoding of emotionally-salient memories, and higher levels of irritability in youth. Lower parietal cortical thickness, greater right fusiform gyral activity,and greater right entorhinal cortical thickness, neural regions with known reciprocal

connections[66,67], may predispose to enhanced processing of ambiguous/threatening emotional faces, greater encoding of emotionally-salient memories, and decreased capacity to regulate these processes, resulting in greater *future irritability* in at-risk youth.

It is unclear why neuroimaging measures of reward, emotion processing, and cortical thickness did not predict *anxiety/depression* factor score. This factor includes just four questions from the CALS and five from the ALS focusing on physiological response to anxious distress and arousal, and thus may represent a non-specific distress measure not associated with the specific neural measures included in the present analyses.

TIME1:*mixed/mania* factor score was a non-zero predictor of future *mixed/mania* factor score. Interestingly, the other TIME1 factor scores did not predict the repeated future factor scores, and age was a non-zero predictor only of future *mixed/mania* factor score. These findings indicate increasing severity of *mixed/mania*, but not *irritability* or *anxiety/depression*, with greater age in BIOS youth, and highlight the importance of the *mixed/mania* factor as a potential risk factor for future BD[14].

Greater self-reported depression, predicted *all three affective lability factors* suggesting, as proposed by the Research Domain Criteria (RDoC), that some constructs, such as depressive symptoms, are common risk factors for different mood and anxiety disorders.

Importantly, we confirmed the validity of the predictor models for each affective lability factor in an independent sample of youth. All three validation models were significant, and explained portions of the variance in outcome measures, particularly for the *mixed/mania* and *irritability* factor scores. Although the majority of the directions of the relationships were consistent across BIOS and LAMS youth, there were some discrepancies. The relationship between left pars orbitalis thickness and future mean *mixed/mania* factor score differed across BIOS and LAMS youth, and was related to TIME1:CALS-P severity in LAMS youth. 65% (35/54) of LAMS youth, but only 15% (6/41) of BIOS youth, had TIME1:CALS-P scores above the normative cutoff, indicating greater illness severity in LAMS youth. LAMS youth with lower CALS-P scores showed the same positive predictive relationship between the two variables as BIOS youth, while LAMS youth with CALS-P scores above the normative cutoff showed a negative relationship between these variables. There were no differences in TIME1 left pars orbitalis thickness between LAMS subgroups, however suggesting subtle differences that warrant further study. Previous findings indicate greater right vlPFC cortical thickness in BD at-risk samples, but lower right vlPFC cortical thickness in individuals with BD, versus healthy individuals [21]. These findings were interpreted as greater cortical thickness being a potential compensation marker in at-risk individuals, with lower cortical thickness reflecting toxicity and illness-related burdens to the prefrontal cortex. Thus, it is possible that toxicity effects of higher CALS-P scores predispose to reduced left pars orbitalis thickness and higher *mixed/mania* factor scores in the future, but this needs to be determined in further studies.

As in BIOS youth, TIME1:age positively predicted *mixed/mania* factor score in low and higher CALS-P LAMS subgroups. In all LAMS youth, the weak negative relationship between these measures is intriguing, and may have resulted from a suppression effect of

another predictor variable on the age-mixed/mania factor relationship[68]. Having an MDD diagnosis predicted greater future *irritability* factor score in the low CALS-P LAMS subgroup, as in BIOS youth, but lower future *irritability* factor score in the higher CALS-P LAMS subgroup. The combination of higher than normative CALS-P score and MDD diagnosis predicting lower future irritability in youth may reflect lower risk for future BD and associated irritability in this LAMS subgroup, but this needs to be replicated [69].

LAMS youth, unlike BIOS youth, showed positive predictive relationships for left precuneus thickness and both future *mixed/mania* and *irritability* factor scores. These findings were not related to CALS-P severity, however, as both LAMS CALS-P subgroups showed positive relationships between left precuneus cortical thickness and factor scores, and had similar left precuneus thickness. This may be related to the effects of psychotropic medications on precuneus function [70–72], as LAMS youth were more likely to be medicated. The absence of an association between future factor scores and amygdala activity may suggest that changes in amygdala activity, rather than baseline amygdala activity, are related to future symptom measures[73]. Further studies are needed to understand the above relationships.

There were limitations to the study. The use of both adult and child versions of the ALS was necessitated by participants aging into adulthood. Independent investigators, however, identified three similar factors within the two scales [10,31]. We focused on measures of reward, emotion processing, and cortical thickness that have shown key relationships with BD development. Other neuroimaging measures, including global measures of cortical thickness and volume, and more refined gray matter structural atlas-defined cortical subregions (e.g. insula) and subcortical regions (e.g. thalamus and striatum) can be neural predictors in future studies. Some of these measures may be related to anxiety/depression factor scores [74–76].

The validation sample was multisite; adding site to the validation model did not improve model fit (all p's>.484). Some participants were medicated. Medication use was not a non-zero predictor of outcomes, however, and was not correlated with outcome variables (all ps>. 347; SI).

We show for the first time that future affective lability factor scores are predicted by unique combinations of clinical measures, cortical thickness and neural activity in both an initial and a second, independent youth sample, regardless of processing methods. In both samples, over one-fourth of the explained variance of *mixed/mania* and *irritability* factors were explained by neural measures, while the *anxiety/depression* factor was not predicted by neural measures utilized in this analysis. Together, our findings across two youth samples suggests that combinations of neural and clinical measures may indicate risk for future BD, and provide neural markers to guide and monitor new, early interventions targeting these markers to improve their effectiveness in BD at-risk youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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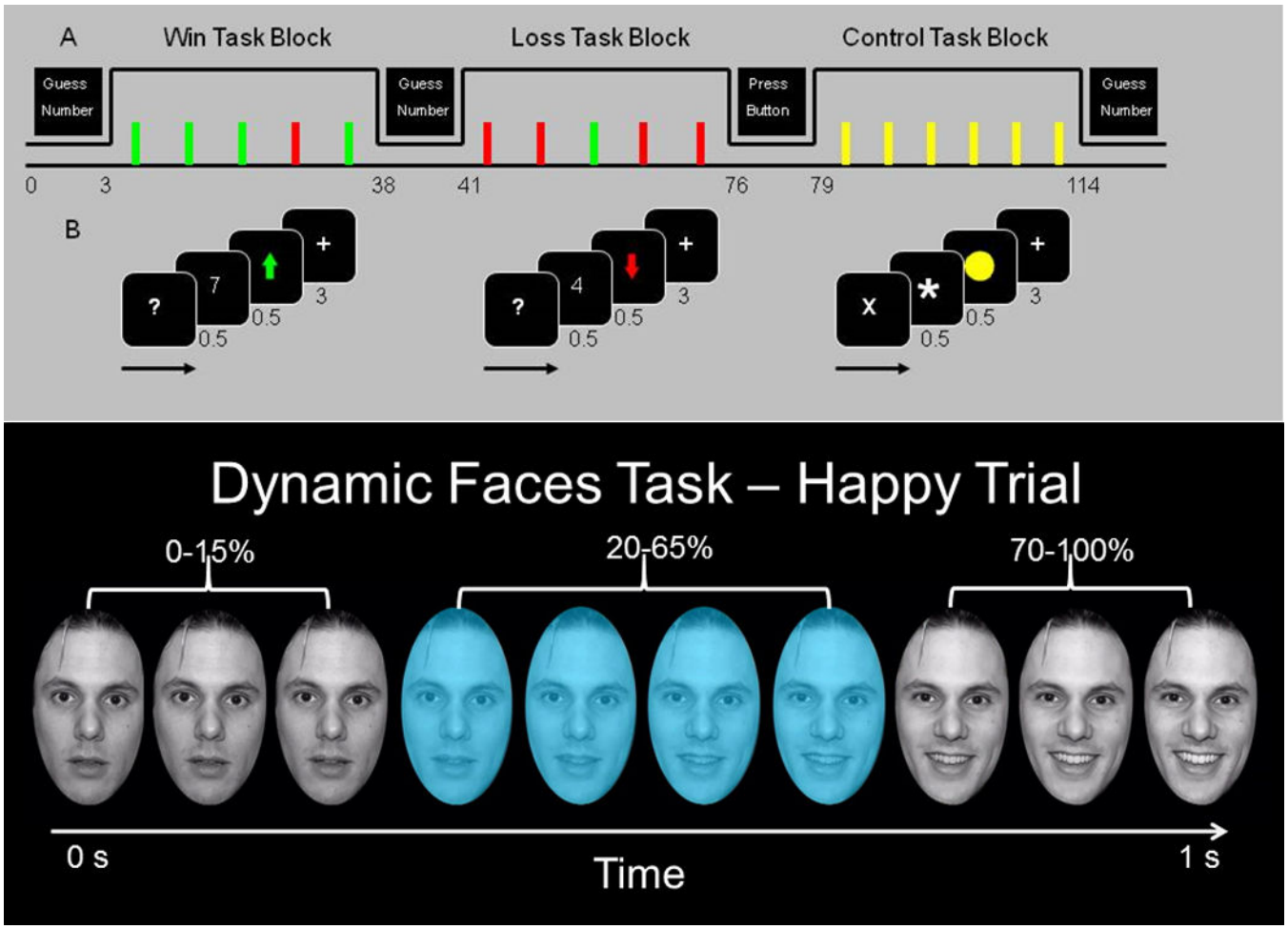
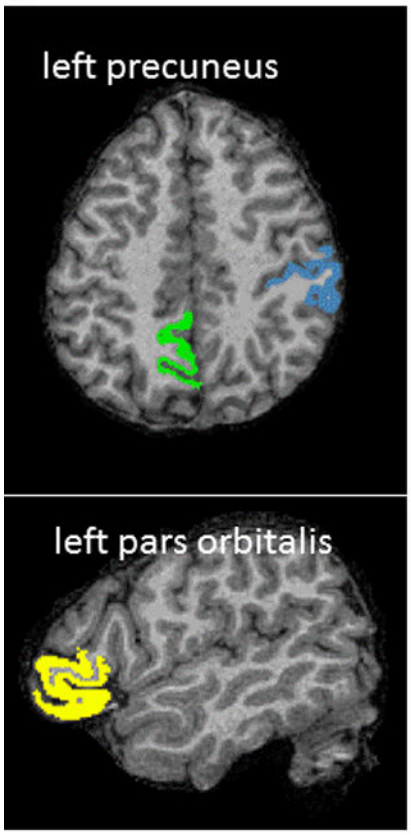


Figure1.

Participants guessed whether a card (value,1–9) was higher/lower than 5, participants then viewed the number, possible outcome (win, green arrow; loss, red arrow),and fixation cross. In control trials, participants pressed a button marked "X," then viewed an asterisk, circle, and fixation cross. 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 six control trials, whereas guessing blocks (Win and Loss) had five trials in an oddball format. **Emotion processing task**[29]: Representation of an emotional face (angry condition) and a shape (control condition) trials of the emotional dynamic faces task. There were 3 blocks for each of the 4 emotional trials with 12 stimuli per block. There were 12 control blocks with 6 stimuli per block. During this task, participants viewed a face changing from a neutral to a happy, sad, angry (depicted here), or fearful emotional expression during a 1000-ms trial. During the control condition, participants viewed a dark grey oval increasing in size during the trial. Participants were required to identify the color of an oval superimposed over both the face and the shape the color was presented between 200 and 650ms of a trial.

A



B.

	LAMS CALS-P score under 9 n=18	LAMS CALS-P score over 9 n=35	statistic	pvalue
age	13.74 (1.6)	13.68 (2.1)	t(53) -.016	0.988
MDD diagnosis (yes)	4/18	11/35	x2= .217	0.641
left precuneus thickness	.97 (.03)	.97 (.05)	t(49.4)=.118	0.891
left pars orbitalis thickness	1.05(.07)	1.06(.09)	t(53)= -.397	0.693

C.

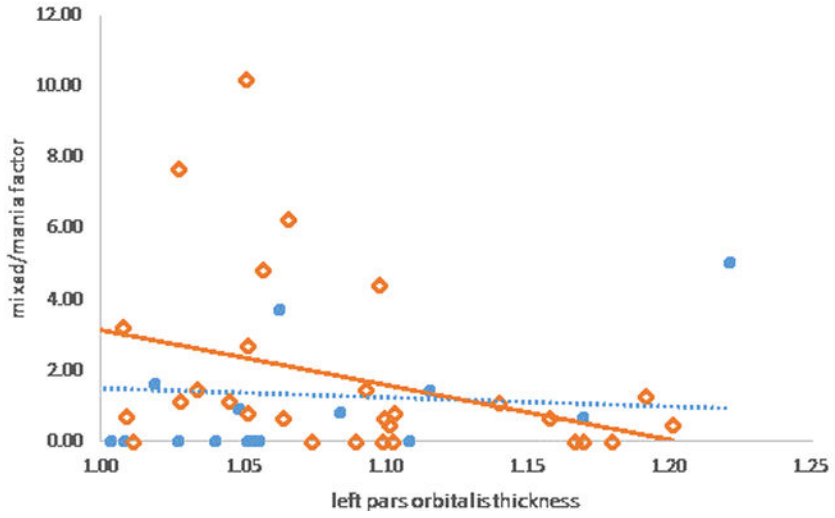


Figure2.

CALS-P relationships. A. Representation of left precuneus and left vlPFC, regions differentially associated with mixed/mania or irritability factor scores. B. Comparison of TIME1:CALS-P normative and higher scores. C. Graphs of left vlPFC thickness -future *mixed/mania* factor score. Circles = participants with TIME1:CALS-P score of 9 or below; Diamonds = participants with TIME1:CALS-P score above 9. Abbreviations: CALS-P = parent report of Child Affective Lability Scale.

Table1.

Clinical and demographic information at time of fMRI scan of BIOS and LAMS samples.

	BIOS n=41	LAMS n=55	Test statistic	p
Age	14 (2.3)	13.7 (1.9)	$t_{(94)} = .575$	.566
Gender (female)	19/41	25/55	χ^2=.007	.931
IQ	102.4 (11.1)	104.3 (13.3)	$t_{(39)} = -.49$	.626
Lifetime Diagnosis				
Depression	4/41	16/55	χ^2=5.3	.021*
Anxiety	8/41	16/55	χ^2=1.15	.2.84
ADHD	6/41	38/55	χ^2=28.1	<.001*
Medication	6/41	37/55	χ^2=24.2	<.001*
Clinical scores at scan				
KMRS	.90 (1.6)	4.2 (6.3)	$t_{(63.346)} = -3.71$	<.001*
KDRS	3.1 (5.9)	3.4 (4.1)	$t_{(94)} = -.261$	.795
CALS	9.2 (12.3)	9.0 (10.6)	$t_{(94)} = -.117$	.907
SCARED	11.0 (11.6)	10.3 (10.1)	$t_{(94)} = .292$	.771
MFQ	9.8 (11.3)	7.9 (7.3)	$t_{(64.4)} = .964$	.339
Days between scan and follow up	899.68 (342.4)	752.6 (193.9)	$t_{(58.9)} = 2.5$	.016*

Abbreviations: Bipolar Offspring Study (BIOS), Longitudinal Assessment of Manic Symptoms study (LAMS), Kiddie Schedule of affective disorders mania rating scale – summary report (KMRS), Kiddie Schedule of affective disorders depression rating scale –summary report (KDRS), Child affect lability scale – child report (CALS), Screen for child anxiety related emotional disorders – child report (SCARED), Mood and feelings questionnaire – child report (MFQ) Numbers refer to mean (standard deviation) or proportion

*<.05

Table 2.

Wholebrain task related activity from emotional face, reward, and loss processing tasks used as predictors in penalized regression models.

	k	MNI			Region	Laterality	Brodmann area
		x	y	z			
Emotional face processing task activity	3306	42	−44	−22	Fusiform	right	37
	2060	−42	−90	−14	Visual association cortex	left	18
	1197	22	−2	−20	Amygdala	right	
	330	−18	−6	−20	Amygdala	left	
	10	−36	−10	−30	Parahippocampus	left	
Reward processing task activity	1131	2	26	44	Superior prefrontal cortex	right	8
	1060	48	−42	48	Parietal cortex	right	40
	570	−40	−60	54	Parietal cortex	left	39
	558	42	28	32	Dorsolateral prefrontal cortex	right	9
	252	−30	22	−4	Insula	left	
	251	4	−16	28	Posterior cingulate cortex	right	23
	224	36	20	2	Insula	right	
	184	30	54	0	Medial prefrontal cortex	right	10
	116	64	−28	−12	Temporal cortex	right	21
	95	−34	54	4	ventromedial prefrontal cortex	left	10
	43	−46	8	36	Superior prefrontal cortex	left	8
	43	−36	−64	−30	Cerebellum	left	
	26	6	−74	46	Parietal cortex	right	7
	15	−38	50	−6	ventromedial prefrontal cortex	left	10
	12	−10	−76	−28	Cerebellum	left	
Loss processing task activity	691	50	−44	48	Parietal cortex	right	40
	483	6	26	44	Superior prefrontal cortex	right	8
	265	44	22	44	Superior prefrontal cortex	right	8
	134	−40	−64	52	Parietal cortex	left	39
	64	36	18	−2	Insula	right	
	37	2	−14	26	Posterior cingulate cortex	right	23
	33	68	−26	−8	Temporal cortex	right	21
	16	−36	−64	−30	Cerebellum	left	
	15	−34	54	4	Medial prefrontal cortex	left	10
	10	−32	52	24	Medial prefrontal cortex	left	10
	10	−30	18	2	Insula	left	

Voxel-wise correction p=.05, cluster correction >10.

Table 3:

Beta coefficients for regularized regression models for BIOS sample. Beta coefficients for GLM regression models for BIOS, LAMS, and split LAMS samples.

A: Mean mania/mixed factor score	Anatomical region	BIOS non-zero variables selected from regularized regression	BIOS regularized regression beta	BIOS standardized beta n=41	LAMS standardized beta n=54	LAMS CALS-P score under 9 n=18	LAMS CALS-P score over 9 n=35
		TIME1:mixed/mania factor score	0.07	0.237	0.432	0.454	0.364
		TIME1:MFQ	0.01	0.228	0.068	−0.635	0.151
		Age	0.0002	0.116	−0.014	0.410	0.053
	vlPFC	left pars orbitalis thickness	0.4	0.258	−0.257	0.037	−0.371
	vlPFC	left pars triangularis thickness	0.46	0.205	0.119	0.885	−0.077
	Parietal cortex	right supramaginal thickness	−0.22	−0.204	−0.043	−0.424	0.011
	Parietal cortex	left precuneus thickness	−0.68	−0.186	0.077	0.305	0.078
	Temporal cortex	left transverse temporal cortex	−0.07	−0.174	−0.123	0.273	−0.245
				F(8,32) = 8.18, p<.001	**F(8,45) = 3.71, p=.002**	F(8,9)=1.18, p=.402	**F(8,26)=3.34, p=.009**
				R2= 67.2	R2= 31.5		
B: Mean irritabilty factor score							
		MDD diagnosis	0.016	0.027	−0.005	0.097	−0.087
		TIME1:MFQ	0.005	0.482	0.543	0.024	0.719
	mni: 42, −44, −22	right fusiform BOLD activity	0.001	0.264	0.184	0.171	0.331
	Medial temporal cortex	right entorhinal cortex	0.213	0.3	0.122	−0.019	0.097
	Parietal cortex	left precuneus	−0.239	−0.122	0.289	0.306	0.310
				F(5.35) = 11.67, p<.001	**F(5.48) = 4.61, p=.002**	F(5,12)=.32, p=.889	**F(5,29)=5.39, p=.001**
				R2 = 62.5	R2 = 32.4		
C: Mean anxiety/ depression factor score							
		TIME1:MFQ	0.005	0.535	0.344		
				F(1.40) = 15.66, p<.001	**F(1,53) = 6.98, p=.011**		

A: Mean mania/mixed factor score	Anatomical region	BIOS non-zero variables selected from regularized regression	BIOS regularized regression beta	BIOS standardized beta n=41	LAMS standardized beta n=54	LAMS CALS-P score under 9 n=18	LAMS CALS-P score over 9 n=35
				R2 = 28.7	R2 = 11.9		