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## Neural Functional Connectivity Changes to Psychosocial Stress in Young Adults with Bipolar Disorder and Preliminary Associations with Clinical Trajectories

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### Abstract

**BACKGROUND:** Stress-related mechanisms are implicated in the pathophysiology of bipolar disorder and may contribute to heterogeneity in illness course. Yet, there is a lack of study investigating the neural mechanisms underlying the stress response in this condition. This study investigated changes in amygdala activation and functional connectivity in response to acute psychosocial stress in young adults with bipolar disorder and explored relations with clinical phenotype and prospective mood symptoms.

**METHODS:** 42 young adults [19 with bipolar disorder, age<sub>mean</sub>± standard deviation=21.4±2.2 years] completed a modified version of the Montreal Imaging Stress Task. Amygdala activation and functional connectivity with prefrontal cortex (PFC) regions of interest was calculated for control and stress conditions. Main effects of group, condition, and group by condition interaction on amygdala activation and connectivity were modeled. A subset of bipolar participants completed one-year follow-up assessments. Relations between neural responses to stress with concurrent substance use and prospective mood symptoms were explored.

**RESULTS:** There were no between-group differences in amygdala activation or functional connectivity during the control condition. Increased right amygdala-right rostral PFC functional

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### DISCLOSURES

We do not believe that any of these relationships could influence the reported results but we report them for transparency. SMS and ETCL received funding for a Janssen-sponsored study through UT. SMS serves as DSMB chair for Sunovion, and served recently on a DMC for Otsuka. He is also a contributor to Medscape. DK, AP, VT, VL, and WAW declare no conflicts of interest.

connectivity to stress was observed in bipolar disorder, compared to typically developing controls. In bipolar disorder, greater increase in right amygdala-right rostral PFC functional connectivity to stress was associated with less frequent cannabis use, and prospectively with shorter duration and lower severity of depression symptoms over follow-up.

**CONCLUSION:** Results from this preliminary study suggest differences in frontolimbic functional connectivity responses to stress in young adults with bipolar disorder and associations with cannabis use and prospective mood symptoms.

### Keywords

bipolar disorder; functional neuroimaging; stress, physiological; amygdala; prefrontal cortex; heart rate; marijuana use

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## INTRODUCTION

Bipolar disorder follows a progressive trajectory, contributing to significant disability, morbidity, and mortality, and exhibits marked heterogeneity in disease course [1, 2]. The neurobiological mechanisms underlying resiliency and vulnerability leading to alternate illness trajectories remain unclear; however, findings from epidemiologic studies suggest psychosocial stress may account for some of the differences in illness progression. Indeed, dysfunction of the stress response is suggested to play a key role in the pathophysiology of bipolar disorder [3]. In bipolar disorder, disruptions in stress response are progressive (i.e. greater dysfunction emerges with age [4]) and have been associated with severity of clinical symptoms (e.g., depression and mania [3]). Recently, studies examining longitudinal outcomes associated with variability in the stress response in bipolar disorder have emerged, and suggest relations with subsequent depressive and manic relapses and worse clinical course [5, 6]. This work has primarily focused on endocrine (i.e. hypothalamic-pituitary-adrenal[HPA] axis) and autonomic (i.e. heart rate) responses to stress [7, 8]. Few studies have investigated the underlying neurobiology that may contribute variation in stress response in bipolar disorder.

The majority of studies investigating neural responses to stress focused on adult samples in the absence of psychiatric illness. These studies suggest differences in amygdala and prefrontal cortex (PFC) activity, as well as amygdala-PFC functional connectivity, may relate to differences in stress response [9–13]. Bipolar disorder is associated with altered development of PFC modulation of limbic regions, i.e., amygdala [14, 15]. Therefore, developmental differences in these brain regions, and their connections, may contribute to differences in neurophysiological responses to stress, and ultimately act as a modulator of illness course. Indeed, the few studies that investigated neural response to stress in bipolar disorder suggest altered amygdala response, compared to healthy subjects [16, 17], and a positive association between amygdala metabolism and cortisol levels in individuals with bipolar disorder [16]. These studies included adults across a wide age range, with one focusing on depressed bipolar adults. It is unclear if altered neurodevelopment of circuits involved in stress response in youth with bipolar disorder [18–20] is associated with differences in stress response early in illness course (and in the absence of depression). Therefore, it is critical to determine whether alterations in neural responses to stress are

present in youth with bipolar disorder, and if these alterations can serve as a modifiable target for early intervention(s).

The current study investigated changes in amygdala activation and amygdala-PFC functional connectivity in young adults with bipolar disorder, compared to typically developing peers (ages 18–25), while participants completed a modified version of the Montreal Imaging Stress Task (MIST)—an acute psychosocial stress functional magnetic resonance imaging (fMRI) task [21, 22]. The study aimed to identify a stable trait marker, specifically altered neural response to psychosocial stress, in young adults with bipolar disorder with no more than mild mood symptoms. PFC regions of interest (ROIs) included the orbitofrontal cortex (OFC) and rostral PFC (rPFC). These regions show changes in activation during psychosocial stress tasks [12, 13, 23] and are implicated in the pathophysiology of bipolar disorder [14, 15, 24, 25]. The OFC is a key region in emotion processing and emotion-guided behavior and is strongly connected with the amygdala via the uncinate fasciculus [26–28]. The rPFC is implicated in the cognitive control of emotional states. The rPFC also shares direct connections with the amygdala (via the uncinate fasciculus), but is thought to be most strongly connected with the amygdala via indirect connections (via other PFC regions and/or through general mechanisms like modulation of neurotransmitter systems) [26–29]. Examination of amygdala functional connectivity with both OFC and rPFC regions allows for investigation of neural responses to stress within both emotional and cognitive systems, as both systems have been related to the stress response [30]. We hypothesized participants with bipolar disorder would exhibit greater increases in amygdala activation in response to stress, compared to typically developing young adults. Additionally, we hypothesized that while the typically developing group would show an increase in negative amygdala-PFC functional coupling in response to stress, the bipolar group would not, suggesting a loss of top-down PFC regulation of the amygdala. Bipolar disorder has been associated with greater prevalence of substance use [31], and substance use has been associated with differences in the stress response [32] and functioning of OFC and rPFC regions [33]. Therefore, we explored associations between neural responses to stress and concurrent alcohol, cannabis, and tobacco use. We also investigated associations between neural responses to stress and prospective mood symptoms over a one-year follow-up period to explore how variation in neural response to stress relates to bipolar illness course. We predicted a greater magnitude of loss of functional coupling between the amygdala-PFC in bipolar disorder would be associated with greater recent substance use and greater duration and severity of mood symptoms during the one-year follow-up.

## METHODS

### Participants and Clinical Data Collection

Forty-eight young adults (24 with bipolar disorder type I and 24 typically developing) were enrolled in the study. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) Research Version (SCID-5-RV) was conducted to assess for diagnosis of bipolar disorder, anxiety disorders, and alcohol/substance use disorders [34]. Current mood symptoms at the time of assessment were determined using the Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS)

[35, 36]. Individuals with moderate/severe mood symptoms (HDRS scores >16; YMRS scores >19) were excluded to investigate a stable trait marker, specifically altered response to psychosocial stress, in individuals with no more than mild mood symptoms. Verbal comprehension and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) were used as a measure of full-scale intelligence quotient (FSIQ-2). For all participants, exclusion criteria included history of any major medical illness with possible neurological or central nervous system outcomes, history of severe alcohol/substance use disorder, IQ<85, being pregnant, or having a medical condition/previous surgery preventing participation in a MRI scan. Individuals with mild or moderate alcohol/substance use disorders were not excluded to increase generalizability of findings [37]. Additional exclusion criteria for typically developing participants included history of mood, psychosis, or anxiety disorders, lifetime suicide attempt, and use of psychotropic medication. Based on these exclusion criteria, six participants (five with bipolar disorder and one typically developing) were excluded from final analysis. Of the five bipolar participants excluded, three had HDRS scores >16 and two had a current severe alcohol use disorder. The typically developing participant excluded from final analysis had an anxiety disorder. Therefore, the final sample included 42 participants (19 with bipolar disorder type 1 and 23 typically developing; see table 1 for demographic and clinical characteristics). Urinalysis was conducted on the day of the scan to assess for pregnancy and substance use. Participants were asked to abstain from any alcohol or drug use for 24-hours preceding the MRI scan. All study procedures were approved by the University of Texas at Austin Institutional Review Board and written consent was obtained from all participants.

### **MRI Acquisition**

High-resolution sagittal structural MRI images were acquired with a three-dimensional gradient echo (MPRAGE) T1-weighted sequence on a 3-Tesla Siemens Skyra (Siemens, Erlangen, Germany) using a 32-channel head coil, and the following parameters: repetition time (TR)=1900ms, echo time (TE)=2.42ms, matrix=224×224, field of view=220×220mm<sup>2</sup>, 192 one-mm slices without gap and one average. fMRI data was acquired with a single-shot echo-planar imaging sequence aligned with the anterior-posterior commissure plane with multiband factor of 3, TR=2000ms, TE=30ms, matrix=128×128, field of view=220 × 220mm<sup>2</sup>, and 72 two-mm slices without gap.

### **Stress Math Task (SMT)**

During fMRI acquisition, participants completed a modified version of the Montreal Imaging Stress Task (MIST) [21, 23], which included a control math task condition and a stress math task condition [38]. The low-stress control condition included easier arithmetic problems with no social evaluation component. All participants completed the control condition first, followed by the stress condition. For the control condition, participants completed 40 different subtraction problems with two answer choices. Events (math problems) were 5 seconds in duration separated by 1.5 second inter-trial intervals (fixation point presented). Participants were told they had five seconds to choose the correct answer via a button box. The stress condition was similar to the control condition, however, participants completed 80 more difficult subtraction problems with three answer choices and were told they had between 1 and 3 seconds to choose their answer. The trial duration

was, however, identical to the control condition (5 seconds). Additionally, participants were presented with six prerecorded negative auditory feedback messages at fixed time points during the stress condition (presented during inter-trial intervals and presented to all participants regardless of performance). Participants' heart rate was recorded throughout the neuroimaging session via an MRI safe pulse oximeter placed on the index finger to assess for physiological response to the stress condition. After completion of the task, all participants were debriefed and told their performance was not evaluated during the task.

### Functional Activation and Connectivity Preprocessing

Statistical Parametric Mapping software (SPM12; <http://www.fil.ion.ucl.ac.uk/spm>) was used to preprocess fMRI data. Data was realigned to correct for inter-scan movements, corrected for within-scan acquisition time differences between slices, coregistered to anatomical data, and spatially normalized to the T1-weighted template image with parameters estimated from segmentation and resampled during normalization. Data was spatially smoothed with a 4mm FWHM Gaussian kernel. A priori bilateral amygdala ROIs were defined using the WFU PickAtlas Tool (<http://www.fmri.wfubmc.edu/download.htm>) in SPM12. At the subject level, event-related response amplitudes were estimated using the general linear model for math problems during the control and stress conditions. Events were defined as onset and duration of each math problem during control and stress conditions (separately) and compared to the inter-trial intervals when a fixation point was presented for 1.5 seconds during the control and stress conditions, respectively. Audio recordings during the stress condition were also modeled so events during the stress condition were only compared to inter-trial intervals when no audio recording was presented. The estimated six parameter spatial transformation (from realignment) was included as a task regressor when modeling control and stress condition events. Event amplitude for bilateral amygdala ROIs was calculated and extracted for both conditions for subsequent statistical analysis.

A functional connectivity analysis was conducted with the CONN toolbox ([www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn) [39]), using a previously described preprocessing utility [40, 41]. The control and stress conditions were manually defined by volumes. For the stress condition, the volumes for the first 40 math problems were manually defined as events of interest to match the control condition, which consisted of 40 math problems. Smoothing was performed during initial reconstruction with a 7mm full-width at half-maximum (FWHM) Hamming filter. Volumes were examined for outliers using the Artifact Detection Tools toolbox contained in CONN. Scrubbing thresholds were set for spikes in global signal equal or greater than 3 standard deviations from the mean and any movement spikes  $> 0.5$ mm. White matter, cerebrospinal fluid, movement parameters, scrubbing, and effects of task conditions were included in our list of confounders. Task condition regressors included control and stress math events (the stress condition math problem events defined separately for first and last 40 math problems) and audio recordings of negative feedback. Quadratic detrending and a high-pass filter was applied at 0.008Hz to remove global low-frequency signals. Bilateral amygdala and OFC ROIs were defined from the FSL Harvard-Oxford Atlas in CONN. Bilateral rPFC ROIs [MNI right center coordinates: (32, 46, 27); MNI left center coordinates: (-32, 45, 27)] came from a pre-defined network atlas in CONN

and were originally derived from an independent component analysis (ICA) based on the Human Connectome Project (HCP) dataset of 497 subjects<sup>[42]</sup>. See Supplemental figure 1 for illustration of ROIs. In CONN, a generalized psychophysiological interaction (gPPI) analysis was used along with a bivariate regression analysis to generate beta values<sup>[43]</sup>. When modeling problems during the stress condition, we did not contrast events of interest to inter-trial intervals that included auditory feedback. Results between each pair of ROIs during the control and stress conditions were converted into Fisher's z-scores and then extracted for further subsequent statistical analysis.

### One-Year Clinical Follow-Up

A subset of participants with bipolar disorder (n=13) completed the Longitudinal Interval Follow-up Evaluation (LIFE) one year following their initial visit<sup>[44]</sup>. This instrument retrospectively collects weekly Psychiatric Status Ratings (PSRs) for depression and mania using a 6-point severity scale (1 = no symptoms, 2–4 = subthreshold symptoms, 5 = meets full threshold DSM-4 criteria for that week, without psychosis or extreme impairment in functioning, 6 = full threshold DSM-4 criteria for that week, with psychosis or extreme impairment in functioning). Number of weeks with depression or manic symptoms along with severity of symptoms experienced (i.e, highest PSR level experienced) were calculated. Presence of suicidal ideation (yes/no) over the follow-up period was assessed.

### Additional Measures Collected

Recent alcohol use was assessed using a modified version of the Daily Drinking Questionnaire (DDQ)<sup>[45]</sup> to assess the heaviest drinking week (DDQ-H) over the past month. Total number of drinks and number of drinking days during heaviest drinking week was calculated. Participants completed a modified version of the Daily Drug-Taking Questionnaire (DDTQ)<sup>[46]</sup> to assess the heaviest drug-taking week (DDTQ-H) over the past month. Number of cannabis and tobacco users per group and number of cannabis use days during heaviest drug-taking week was measured.

### Statistical Analyses

**Between-Group Differences in Demographics and Clinical Factors**—Between group differences in the continuous demographic and clinical variables were assessed with a t-test or Wilcoxon test, as appropriate, and included age, IQ, total days drinking and total drinks during heaviest drinking week, total days using cannabis during heaviest using week, mood symptoms over past week (HDRS, YMRS), and time of neuroimaging session. Between group differences in categorical variables were assessed with Chi square or Fisher's exact test, as appropriate, and included sex, history/current alcohol or substance use disorders, past month cannabis and tobacco users, and urine toxicology for drugs of abuse.

**fMRI Stress Math Task: Heart Rate and Task Performance Analysis**—Average heart rate for the control and stress conditions was calculated and main effects of group (bipolar, typically developing), condition (control, stress), and group by condition interactions were modeled, with condition as a repeated within-subject variable. We were unable to collect pulse data on seven participants (two with bipolar disorder and five typically developing participants) owing to an error in the pulse hoc software during data

collection. Similar models were used to evaluate behavioral performance during the control and stress math conditions. Specifically, effects of group, condition, and group by condition interactions were modeled, with condition a repeated within-subject variable, and accuracy (number of incorrect responses) or response time (average reaction time for math problems) as the dependent variable.

**Neural Responses to Stress Math Task**—Between group differences in left and right amygdala activation (modeled separately) were investigated during the control condition alone with a two-tailed *t* test. To investigate changes in response to stress, main effects of group, condition, and group by condition interactions were modeled, with condition as a repeated within subject variable and amygdala activation during the control and stress condition as the dependent variables. Parallel models were conducted to assess stress-associated differences in amygdala functional connectivity with *a priori* ROIs, with fisher-transformed z-scores between amygdala and OFC or rPFC ROIs as the dependent variables. Following a significant group by condition interaction, models were repeated stratified by group. For these planned analyses, significance was defined as  $\alpha < .025$  for amygdala activation (Bonferroni correction to account for two comparisons: investigation of left and right amygdala) and  $\alpha < .0125$  for amygdala functional connectivity models (Bonferroni correction to account for four comparisons: investigation of amygdala connectivity with OFC and rPFC bilaterally). Only within hemisphere connections were investigated to decrease number of comparisons. All analyses were repeated with task accuracy during the stress condition included as a covariate to examine the effect of increased cognitive load during the stress condition and determine if activation/functional connectivity is related to task accuracy.

### Exploratory Analyses

**Relations Between Neural Responses to Stress Math Task and Concurrent Alcohol, Cannabis, and Tobacco Use:** Change in amygdala activation or amygdala functional connectivity with ROIs (that showed a significant group by condition interaction or main effect of condition in the primary model) were calculated for each bipolar disorder participant, e.g., amygdala activation stress condition minus amygdala activation control condition. Pearson or spearman correlations, as appropriate, were used to explore relations between change in amygdala activation or amygdala functional connectivity with recent alcohol and cannabis use in bipolar disorder. A two-tailed t-test was used to explore differences between bipolar participants with/without past month tobacco use. Significance was set at  $\alpha = .05$  for these exploratory *a priori* analyses. Following a significant association between amygdala activation or amygdala connectivity and alcohol/cannabis use, sensitivity analyses were conducted modeling the main effects of groups, condition, and group by condition interactions, as above, while including substance use measure that showed an association with neural response to stress as a covariate.

### **Relations Between Neural Responses to Stress Math Task and Prospective Mood**

**Symptoms:** To explore relations with prospective mood symptoms in the bipolar disorder group, Pearson correlations were used to examine associations between changes in neural responses to stress (i.e., ROI-ROI pairs showing a significant effect of condition or group by

condition interaction in the primary model) with prospective mood symptoms, specifically duration (number of weeks with depression or mania symptoms) and highest severity (i.e., PSR) of depression or mania symptoms experienced during the one-year follow-up period. For exploratory analyses significance was set at alpha .05.

## RESULTS

### Demographic and Clinical Factor Analyses

The bipolar disorder group showed greater HDRS scores and had more individuals who used tobacco over the past month, compared to the typically developing group. No other between group differences were observed (see table 1).

### fMRI Stress Math Task: Heart Rate and Task Performance Analysis

Across all participants, heart rate and response time increased during the stress condition, compared to control condition, while accuracy decreased. Additionally, there was a main effect of group on accuracy, with bipolar participants getting more problems incorrect. No group by condition interactions were observed on heart rate or task performance. See table 2 for model statistics.

### Neural Responses to Stress Math Task

**Amygdala Activation**—There was no significant main effect of group or condition, or group by condition interaction, on amygdala activation. There were no between-group differences in amygdala activation during the control condition. When including task accuracy during the stress condition in the model, we observed a significant main effect of condition on change in right amygdala activation, such that activation decreased in response to the stress condition ( $p=0.01$ , Cohen's  $d=0.8$ ). There was also a significant condition by task accuracy interaction such that increase in amygdala activation in response to the stress condition related to a greater number of incorrect responses during the stress condition ( $p=0.01$ ). No interactions with group were observed.

**Functional Connectivity ROI-ROI Analysis**—A significant group by condition interaction was observed for change in functional connectivity between right amygdala-right rPFC ( $p=0.003$ , Cohen's  $d=1.0$ ). When stratifying by group, those with bipolar disorder showed a significant increase in positive functional connectivity between right amygdala-right rPFC ( $p=0.004$ ,  $d=0.8$ ; figure 1) in response to the stress condition, while the typically developing group did not show a change in connectivity ( $p=0.7$ ,  $d=0.1$ ). The group by condition interaction on change in functional connectivity between right amygdala-right rPFC remained significant when including task accuracy as a covariate ( $p=0.003$ ). The stress condition was associated with increased positive functional connectivity between the right amygdala-right OFC and left amygdala-left rPFC across all participants (main effect of condition:  $p=0.03$ ), but these results did not survive Bonferroni correction and were no longer significant when including stress condition task accuracy in the model.

## Exploratory Analyses

### **Relations between Neural Responses to Stress Math Task and Concurrent**

**Alcohol, Cannabis, and Tobacco Use**—In bipolar disorder, increases in right amygdala-right rPFC functional connectivity in response to the stress condition correlated with fewer days of cannabis use during heaviest cannabis use week. ( $\rho=-0.6$ ,  $p=0.008$ ). The group by condition interaction observed for change in right amygdala-right rPFC functional connectivity remained significant when covarying frequency of cannabis use.

### **Relations Between Neural Responses to Stress Math Task and Prospective**

**Mood Symptoms**—In bipolar disorder, increases in functional connectivity between the right amygdala-right rPFC in response to the stress condition correlated with fewer weeks with depression symptoms ( $r=-0.5$ ,  $p=0.05$ ) and less severe depression symptoms experienced ( $r=-0.6$ ,  $p=0.05$ ) during the one-year follow-up period (figure 2).

## DISCUSSION

The current study was designed to assess amygdala activation and functional connectivity changes in response to acute psychosocial stress within bipolar disorder and typically developing young adults. Young adults with bipolar disorder, compared to typically developing peers, showed an increase in functional connectivity between right amygdala-right rPFC in response to the stress condition. Though direction of findings are opposite to what we predicted, findings do suggest that differences in neural responses to stress are evident in young adults with bipolar disorder, i.e., earlier in illness course than previously investigated. Additionally, exploratory findings support our hypothesis that neural responses to stress early in the course of illness are associated with clinical features and prospective clinical trajectories. Specifically, increased functional connectivity between right amygdala-right rPFC in bipolar disorder was associated with less frequent cannabis use and prospectively with shorter duration and less severe of depression symptoms over a one-year follow-up period. Exploratory findings should be interpreted with caution. However, results may suggest increased functional coupling between amygdala and rPFC is associated with compensation of early deficits within the frontolimbic system, and youth unable to compensate are at greatest risk for more frequent and severe mood symptoms. These preliminary results support additional work investigating how variability in neural response to stress, early in the course of bipolar illness, can inform early intervention.

The PFC is thought to exert regulatory control of stress response through its reciprocal direct and indirect connections with the amygdala [47, 48]. While negative amygdala-PFC—particularly ventrolateral PFC—functional connectivity in response to stress has frequently been reported in healthy adults and in adults with bipolar disorder [49, 50], several studies have observed increased amygdala-PFC—both ventrolateral and medial PFC—functional connectivity during emotion and stress regulation in youth with bipolar spectrum disorders and in typically developing young adults, respectively [51, 52]. Additionally, another study in typically developing young adults reported amygdala connectivity with a rPFC region (i.e., pregenual anterior cingulate cortex) associated with executive processes positively varied with psychological stressor-evoked blood pressure reactivity [9]. Indeed, rPFC regional

activation has been observed during emotional Stroop paradigms, with regional engagement posited to represent the exertion of cognitive control over emotional distractors [28, 53]. The amygdala shares fewer direct connections with rPFC regions, relative to OFC regions, and it has been suggested the amygdala and rPFC likely communicate through indirect connections (i.e., via other PFC regions and/or through general mechanisms like modulation of neurotransmitter systems) [26–29]. Our finding of increased amygdala-rPFC functional connectivity could suggest greater recruitment of cognitive control system regions is required during stressful conditions early in the course of bipolar disorder. We found greater recruitment of rPFC was associated with better clinical outcomes (i.e., decreased depression symptoms in a subset of individuals with longitudinal data), however, we cannot discern if functional connectivity changes are compensatory, nor can we determine the long-term consequences of this connectivity pattern. As bipolar disorder, including abnormalities in the rPFC and stress response (i.e. HPA axis) in bipolar disorder, is progressive [3, 4, 18, 19, 25], more work investigating long-term consequences of rPFC recruitment in response to stress is needed. Additionally, increased amygdala-rPFC connectivity to stress was associated with lower frequency of cannabis use. While cannabis use disorder has been associated with worse clinical phenotypes [54], this study cannot discern directionality of this relationship, i.e., if cannabis use contributes to a loss of recruitment of rPFC during stress conditions or if youth with bipolar disorder may use cannabis as a means to cope with stress-related experiences. As findings remained significant when covarying cannabis use days, and variation in structure of both OFC and rostral PFC have been suggested to prospectively predict initiation and development of alcohol/cannabis use in young adults with bipolar disorder [55], these structural differences and associated risk for development of alcohol/cannabis use may relate to the roles of these regions in stress response. Further longitudinal study, with increased power, is critical to disentangle the long-term impact of variation in neural responses to stress, changes over time in stress response, and etiological mechanism(s) that may contribute to variation in stress response.

Changes in neural connectivity could be related to increased cognitive load of the stress condition. In an attempt to explore this, we re-ran our models including task accuracy during the stress condition as a covariate. When controlling for task accuracy, right amygdala – right rPFC functional connectivity results remained significant. Interestingly, a significant main effect of condition on change in amygdala activation to the stress condition emerged such that right amygdala activation decreased in response to the stress condition across both groups. Amygdala activation has been positively associated with cortisol levels during stress in bipolar disorder [16]. Indeed, amygdala activity is thought to increase HPA axis activity via excitatory projections to the paraventricular nucleus [56]. While speculative, decreased amygdala activation to the stress condition may be associated with HPA axis regulation and ultimately suppression of stress-associated cognitive/task performance interference. Supporting this interpretation, we found variation in amygdala activation changes to the stress condition related to differences in task accuracy; an increase in amygdala activation in response to the stress condition was associated with a greater number of incorrect responses. It is possible increased amygdala activation (and less stress regulation) contributed to worse task performance. While directionality of findings cannot be determined, a greater stress response (i.e., higher post-dexamethasone cortisol levels) has been suggested to interfere

with cognitive functioning in bipolar disorder [3, 57]. Additional work examining how stress impacts cognitive processes, including factors that may mediate this relation, is needed. A recent meta-analysis indicated lateral and medial PFC regions have distinct patterns of connectivity (i.e., medial PFC coactivates with autonomic and limbic regions, while lateral PFC coactivates with regions involved in cognitive functions) [58]. Given the cognitive nature of the task, the current study focused on lateral regions. Future studies, however, should examine both lateral and medial PFC regions during stressful cognitive tasks, as this may further our understanding of stress-cognition interactions.

Contrary to our hypothesis, we did not observe group differences in amygdala activation. Several factors, including psychotropic medications and euthymic mood state, may have contributed to this null finding. The majority (76%) of individuals in the bipolar disorder group reported psychotropic medication use at time of scan. Psychotropic medications appear to “normalize” brain activity and have been found to minimize differences in brain activity—including in the amygdala—between individuals with bipolar disorder and healthy individuals [59, 60]. Amygdala activation in response to psychosocial stress in bipolar disorder may be state-dependent. Indeed, studies have shown amygdala activation, including regional responses to acute stress, varies as a function of mood state [15, 61]. While focusing on individuals with only mild mood symptoms decreased sample heterogeneity, excluding individuals with current depressive or manic symptoms may limit generalizability of findings. Future studies should use within-subjects longitudinal neuroimaging designs to investigate how functional differences in the stress response in bipolar disorder change in response to treatment and as a function of mood state.

Several limitations should be noted. Findings from this preliminary study should be interpreted with caution owing to small sample size. In light of the sex differences observed in stress response [62], it should be noted that females constituted the majority of our sample, and we were underpowered to explore sex differences. Young adults with bipolar disorder reported greater past month tobacco use compared to typically developing young adults. While underpowered to investigate impact of tobacco use, an exploratory analysis suggested bipolar young adults reporting past month tobacco use did not significantly differ from those not reporting past month tobacco use in changes in right amygdala - rPFC functional connectivity. Future work should explore the potential impact of tobacco use—and polysubstance use—on stress response in bipolar disorder. The stress condition included auditory feedback while the control condition did not. Though the auditory feedback occurred during inter-trial intervals and was excluded from analysis, we cannot exclude the possibility that audio feedback impacted findings. While both groups showed similar physiological responses to the task (i.e., both groups showed increase in heart rate), it is possible groups differed in how stressful they perceived the stress math task. Future studies should incorporate other physiological/hormonal measures, including heart rate variability and stress hormone assessment. For example, differences in heart rate variability are reported in bipolar disorder, [63] with reduced heart rate variability suggested to relate to greater illness burden [64]. While change in heart rate did not differ between groups, heart rate variability may differ in response to stress, with variation in heart rate variability a possible biomarker for alcohol/substance use disorders [65]. Due to limited power, longitudinal findings should be considered preliminary and hypothesis generating.

Potential differences may exist in individuals with, compared to those without, longitudinal data that could have biased results. However, when comparing bipolar participants with longitudinal data to those without, there was no difference in clinical and demographic factors of interest or neural responses to the stress math condition. This preliminary study suggests future longitudinal studies in this area are needed with the power to investigate sex differences, effects of psychotropic medication, changes in neural responses to stress over time, associated cortisol/physiological response [66], and clinical trajectories in bipolar disorder.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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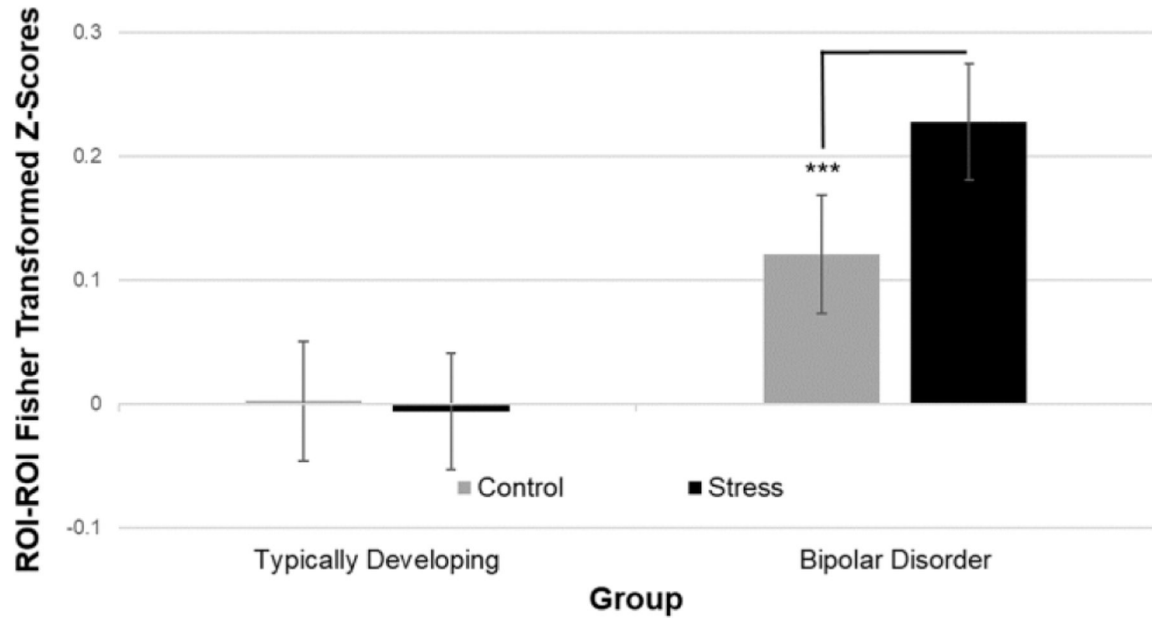
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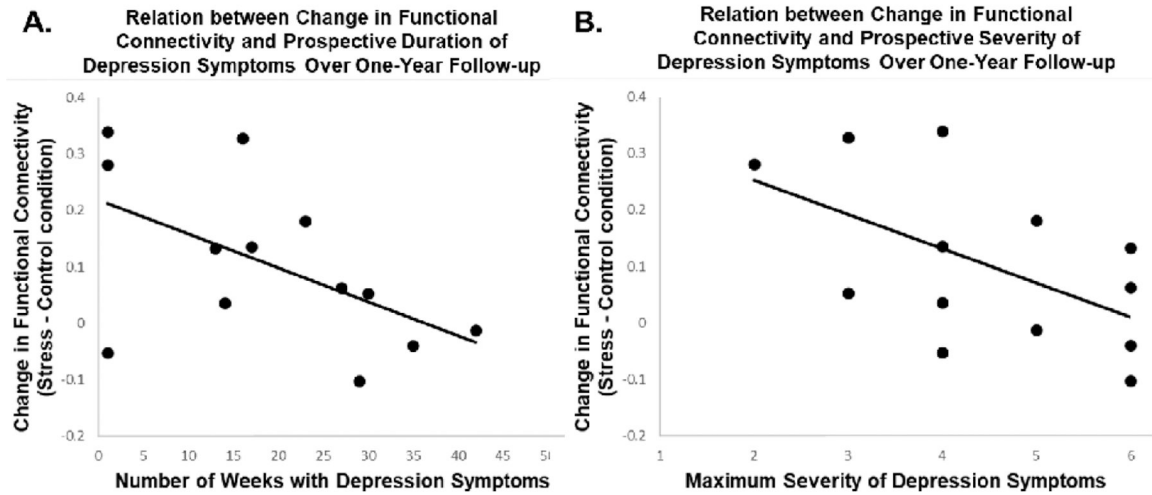
## Right Amygdala – Right Rostral Prefrontal Cortex Functional Connectivity during Stress Math Task: Control and Stress Conditions



**Figure 1. Neural functional connectivity changes in right amygdala - right rostral prefrontal cortex during the Stress Math Task**

Mean functional connectivity between right amygdala - right rostral prefrontal cortex in young adults with bipolar disorder and typically developing controls in response to control and stress math conditions. There was a significant condition by group interaction ( $p=0.003$ ) with bipolar disorder young adults showing increased positive functional connectivity of right amygdala - right rostral prefrontal cortex during the stress condition, compared to the control condition. Typically developing controls did not show changes in functional connectivity between the right amygdala-right rostral prefrontal cortex during the task. Error bars represent standard errors. ROI = region of interest. \*\*\*= $p<.005$ .

## Right Amygdala – Right Rostral Prefrontal Cortex Functional Connectivity and Recurrent Depression Symptoms in Bipolar Disorder



**Figure 2. Relations between right amygdala – right rostral prefrontal cortex functional connectivity changes to stress condition and recurrent depression symptoms over a one-year follow-up period in bipolar disorder**

Preliminary data exploring relations between changes in neural functional connectivity with subsequent depression symptoms in young adults with bipolar disorder indicate greater right amygdala – right rostral prefrontal cortex functional coupling to the stress condition is associated with (A) less frequent and (B) less severe depression symptoms over a one-year follow-up period. Specifically, significant negative correlations were observed between change in right amygdala – right rostral prefrontal cortex functional connectivity to the stress condition (stress condition minus control condition) and the number of weeks in which depression symptoms were experienced ( $r=-0.5$ ,  $p .05$ ) as well as the maximum severity of depression symptoms experienced ( $r=-0.6$ ,  $p .05$ ).

**Table 1.**

## Demographic and clinical factors stratified by group

	Typically developing (N=23)	Bipolar disorder (N=19)	p-value
<b>Demographics</b>			
Mean Age (SD)	21.1 (1.9)	21.4 (2.2)	0.62
Number of Females (%)	16 (70)	14 (74)	1.00 <sup>f</sup>
Mean WASI-II FSIQ-2 <sup>g</sup> (SD)	119 (12)	116 (9)	0.36
<b>Clinical Mood Symptoms</b>			
HDRS <sup>b</sup> (SD)	2 (3)	9 (4)	<0.0001 <sup>Z</sup>
YMRS <sup>c</sup> (SD)	1 (1)	1 (3)	0.72 <sup>Z</sup>
<b>Neuroimaging fMRI Session Time of Day</b>			
Mean Military Time	12:27 (3:05)	12:21 (2:35)	0.97 <sup>Z</sup>
<b>Alcohol/Cannabis Use Disorders</b>			
Past Alcohol Use Disorder, mild (%)	2 (9)	4 (21)	0.38 <sup>f</sup>
Current Cannabis Use Disorder, mild (%)	2 (9)	3 (16)	0.64 <sup>f</sup>
Current Cannabis Use Disorder, moderate (%)	1 (4)	0 (0)	1.00 <sup>f</sup>
Past Cannabis Use Disorder, mild (%)	0 (0)	1 (5)	0.45 <sup>f</sup>
<b>Past Month Alcohol/Cannabis Use</b>			
Total Drinks <sup>d</sup> (SD)	10.9 (7.6)	8.7 (7.8)	0.38
Number of Drinking Days <sup>d</sup> (SD)	2.6 (2)	2.8 (2)	0.71
Cannabis Users <sup>e</sup> (%)	7 (30)	10 (53)	0.14
Number of Cannabis Use Days <sup>g</sup> (SD)	3.7 (2.9)	4.1 (2.9)	0.80 <sup>Z</sup>
Tobacco Users <sup>e</sup> (%)	1 (0.04)	6 (32)	0.03 <sup>f</sup>
<b>Positive Urinalysis Toxicology Screen</b>			
Tetrahydrocannabinol (%)	5 (22)	6 (32)	0.50 <sup>f</sup>
Amphetamines (%)	1 (4)	2 (11)	0.58 <sup>f</sup>
Benzodiazepines (%)	1 (4)	1 (5)	1.00 <sup>f</sup>
Phencyclidines (%)	0 (0)	1 (5)	0.45 <sup>f</sup>
<b>Other Clinical Factors and Comorbidities</b>			
Illness Duration <sup>h</sup> (SD)	N/A	3.7 (2.1)	N/A
Rapid Cycling <sup>i</sup> (%)	N/A	6 (32)	N/A
Lifetime Psychosis (%)	N/A	8 (42)	N/A
Lifetime suicide attempt (%)	N/A	6 (32)	N/A
Comorbid Anxiety Disorders <sup>j</sup> (%)	N/A	7 (37)	N/A
<b>Medications</b>			
Unmedicated at scan (%)	N/A	5 (26)	N/A

	Typically developing (N=23)	Bipolar disorder (N=19)	p-value
Antipsychotic (%)	N/A	7 (37)	N/A
Anticonvulsant (%)	N/A	4 (21)	N/A
Antidepressant / SSRIs (%)	N/A	3 (16)	N/A
Stimulant (%)	N/A	1 (5)	N/A
Lithium (%)	N/A	8 (42)	N/A
Anxiolytics (%)	N/A	3 (16)	N/A
Sedatives/Antihistamines (%)	N/A	3 (16)	N/A
Prazosin (%)	N/A	2 (11)	N/A

Between-group (bipolar disorder vs. typically developing) differences in age FSIQ-2, Total Drinks/Heaviest Drinking Week, Number of Drinking Days/Heaviest Drinking Week were compared using a two-sample t-test. All other factors were examined with a Mann-Whitney-Wilcoxon or Fisher Exact tests, as appropriate. Between-group differences in rapid cycling, lifetime psychosis, lifetime suicide attempt, comorbid anxiety disorders, and psychotropic medications were not assessed because these factors were considered an exclusion criterion, and thus not present, in the typically developing group.

<sup>f</sup> represents p-value calculated with Fisher exact test.

<sup>z</sup> represents p-value calculated with a Mann-Whitney-Wilcoxon Test.

<sup>a</sup> FSIQ-2 represents the composite score for the full-scale intelligence quotient comprising verbal comprehension and matrix reasoning subtests on the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II).

<sup>b</sup> Past week depression symptoms were measured using the Hamilton Depression Rating Scale (HDRS).

<sup>c</sup> Past week mania symptoms were measured using the Young Mania Rating Scale (YMRS).

<sup>d</sup> Recent alcohol use was measured with the Daily Drinking Questionnaire adapted for the heaviest week over the past 30 days (DDQ-H).

<sup>e</sup> Recent cannabis and tobacco use was measured with the Daily Drug-Taking Questionnaire adapted for the heaviest week over the past 30 days (DDTQ-H).

<sup>g</sup> Mean number of cannabis use days in individuals reporting past month cannabis use.

<sup>h</sup> Illness Duration was determined by calculating the time (years) between first manic episode and age at fMRI scan.

<sup>i</sup> Rapid Cycling reflects past-year rapid cycling in bipolar disorder participants.

<sup>j</sup> Comorbid anxiety disorders included generalized anxiety disorder and panic disorder.

**Table 2.**

Heart rate and behavioral performance during the Control and Stress Math Conditions

	Control Math Task		Stress Math Task		Effect of Task Condition		Effect of Group	
	TD	BD	TD	BD	F Statistic	p-value	F Statistic	p-value
<b>Heart Rate (bpm)</b>	72 (11)	74 (10)	77 (13)	77 (13)	11.4	0.002	0.08	0.8
<b>Response time (ms)</b>	1925 (455)	2161 (448)	3120 (615)	3141 (593)	193.6	0.0001	0.5	0.5
<b>Math accuracy (No. incorrect)</b>	2 (1)	3 (2)	13 (7)	17 (5)	181.9	0.0001	4.8	0.04

Physiologic and behavioral response to math control and stress tasks separated by typically developing (TD) and bipolar disorder (BD) participant with (standard deviation). Pulse data was collected in thirty-seven participants (17 bipolar and 18 typically developing participants).

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