Published in final edited form as:

Bipolar Disord. 2018 May ; 20(3): 238–247. doi:10.1111/bdi.12583.

Cognitive Control under Stressful Conditions in Transitional Age Youth with Bipolar Disorder: Diagnostic and Sleep-Related Differences in Fronto-Limbic Activation Patterns

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Abstract

Objectives—Adults with bipolar disorder (BD) display aberrant activation in fronto-limbic neural circuitry during cognitive control. However, fronto-limbic response to cognitive control, and factors destabilizing this circuitry, remain under-studied during the transition from adolescence to young adulthood in BD. Sleep patterns are disturbed in BD, undergo change in adolescence, and support brain function. Among transitional age youth, BD diagnosis and sleep (duration and variability) were tested as predictors of fronto-limbic response to a stressful cognitive control task.

Methods—Two groups of youth(13-22yr) participated: 15 with BD type I, II or NOS (BD;age=18.1±2.7years; 11 female) and 25 healthy controls (CTL;age=19.4±2.7years; 17 female). Sleep was monitored with actigraphy for at least 1-week prior to an adaptive multi-source interference fMRI paradigm (a Stroop-like cognitive interference task). Group status and sleep duration (average and intra-individual variability) were examined as predictors of activation to incongruent>congruent trials within bilateral amygdala, anterior cingulate (ACC), ventrolateral prefrontal and dorsolateral prefrontal cortical regions-of-interest.

Results—BD displayed greater right amygdala activation than CTL. Average sleep duration and rostroventral ACC(rvACC) activity were negatively associated in CTL, but exhibited a quadratic relationship in BD such that short and long sleep were related greater rvACC activation. Sleep duration variability and dorsal ACC activity were negatively associated in BD, and unrelated in CTL. Findings remained significant after controlling for age, sex, and mood symptoms.

Conclusions—BD displayed hyper-limbic response during cognitive control, and sleep was a source of variability in ACC engagement. Stabilizing sleep may be one avenue for improving cognitive control in BD.

Keywords

Bipolar Disorder; fMRI; Cognitive Control; Sleep; Stress; Actigraphy

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Dr. Soehner, Dr. Goldstein, Miss Gratzmiller, Dr. Phillips, and Dr. Franzen have no biomedical financial interests or potential conflicts of interest.

Introduction

Aberrant activations within fronto-limbic neural circuitry during emotional and non-emotional tasks of cognitive control are proposed to partially underlie the emotion regulation deficits central to bipolar disorder (BD)¹⁻⁵. Though a recent meta-analysis identified important developmental differences in BOLD response to both emotional and non-emotional fMRI tasks among pediatric versus adult BD samples², few fMRI studies of cognitive control have been conducted during the transition from adolescence to young adulthood in BD. Furthermore, it is unclear which modifiable factors may contribute to inter-individual variability in neural circuits supporting cognitive control in BD. Such factors are particularly critical to understand for adolescents with BD, who are at risk for a more negative course of BD^{6, 7} and are still undergoing development of prefrontal cortical regions supporting cognitive control capacities⁸. The present study investigates how brain function in transitional age youth with and without BD may differ during cognitive control under stressful conditions, and whether sleep duration and stability may contribute to inter-individual differences in brain function.

Fronto-limbic regions implicated in cognitive control in BD include ventral and dorsal aspects of the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), ventrolateral PFC (VLPFC), and amygdala¹. The ACC is a key region in the processing of cognitively-demanding information; it has been associated with response selection, conflict-monitoring, inhibition, and attention^{9, 10}. Lateral PFC regions (e.g., VLPFC, DLPFC) share connections with the ACC, and are implicated in regulatory control¹¹. Amygdala hyper-activation during cognitive processing has been proposed to reflect heightened perception of emotional salience in non-emotional contexts in BD¹. Neuroimaging studies using Stroop-like tasks in adult BD report functional abnormalities predominantly in ventral portions of the lateral PFC and ACC, as well as the amygdala¹¹⁻¹⁸; this ventral prefrontal cortical-limbic dysfunction present in adults with BD appears to be independent of mood state¹⁹. The few studies of cognitive control in pediatric BD have observed similar activation patterns^{14, 17}, which also align with meta-analytic findings in BD across emotional and non-emotional tasks². Namely, that relative to healthy youth, those with BD exhibit amygdala hyper-activation during emotional tasks and ventral ACC hypo-activation during emotional and non-emotional tasks².

A separate line of work suggests that sleep disturbances are a core feature of BD²⁰. Manic episodes are marked by a reduced need for sleep and depressive episodes are characterized by insomnia and/or hypersomnia²¹. Even between mood episodes, significant sleep disturbance persists in up to 70% of BD patients²² and contributes to functional impairment²³. Recent meta-analytic findings indicate that elevated day-to-day variability in sleep patterns are characteristic of BD²². Moreover, above the effects of average sleep duration, variability in sleep duration has been linked to mood disturbance, impaired functioning, and poorer medication adherence in BD^{24, 25}.

It has been proposed that sleep disturbances may be an important source of inter-individual variability in brain function in BD^{26, 27}, thus contributing to heterogeneity in the BD neuroimaging literature. Experimental sleep deprivation fMRI studies in healthy samples

indicate that dorsal prefrontal cortical regions are susceptible to the effects of sleep loss during attentional/cognitive control tasks²⁸, while the amygdala and ventral PFC are affected in emotional tasks²⁹. Sleep deprivation and other sleep disturbances in BD may destabilize fronto-limbic circuitry in BD by amplifying ventral PFC-limbic activation and concomitantly decreasing dorsal PFC activation²⁷. A preliminary study in adult BD examined actigraphy-assessed sleep and activity patterns in relation to brain activations during a working memory fMRI task. They observed that unstable rest-activity patterns, but not sleep duration, predicted DLPFC activation³⁰. In a preliminary study of youth at-risk for BD, sleep duration in the week prior to scan was positively related to ACC activation to rewards, while the opposite association was observed in the comparison group³¹. To date, there is preliminary evidence that sleep duration and variability may be relevant to PFC function in BD, though this remains underexamined. Understanding such processes may be particularly salient to transitional age youth with BD, as this developmental window is characterized by decreasing sleep duration and increasing sleep variability³².

The goal of this study was to test associations between diagnostic status, sleep duration (average and variability), and fronto-limbic neural circuitry function supporting cognitive control in transitional age youth who were psychiatrically healthy (CTL; N=25) or diagnosed with BD (N=15). Youth completed an adaptive version of the Multi-Source Interference fMRI paradigm (MSIT), a stressful cognitive interference task that reliably engages key prefrontal cortical regions implicated in attentional/cognitive control (e.g., dorsal ACC[dACC], DLPFC, VLPFC), and traditionally deactivates limbic regions (e.g., ventral ACC[vACC], amygdala)³⁸. Sleep was behaviorally assessed with actigraphy for 7-14 days prior to scan. The primary aim was to test (a) the effect of BD diagnosis and (b) the effect of sleep duration (mean and variability) on inter-individual differences in BOLD response to incongruent vs. congruent (difficult vs. easy) blocks of MSIT trials. Due to the small sample size, any significant effects of group and, especially, sleep on brain function should be interpreted as preliminary. We hypothesized that (a) relative to CTL, BD would display altered ventral PFC response (vACC, VLPFC) and elevated amygdala response and (b) that sleep duration variables would be related to within-group inter-individual differences in BOLD response in dorsal PFC regions (dACC, DLPFC).

Materials and Methods

Participants

This study was approved by the Institutional Review Board of the University of Pittsburgh and all participants provided written informed assent/consent as appropriate. Two groups of participants 13-22 years-old were recruited from a larger naturalistic study of suicide and sleep in BD: a bipolar disorder group (BD; N=15) and a healthy control group (CTL; N=25). Exclusion criteria for all participants included: 1) left-handedness; 2) claustrophobia; 3) metallic foreign objects in their body; 4) pregnancy; 5) head trauma with any loss of consciousness; 6) pervasive developmental disorder or organic central nervous system disorder; 7) sleep disordered breathing (i.e., an apnea-hypopnea index > 15 events per hour of sleep as assessed by an ApneaLink device [ResMed, San Diego, CA] completed in most

participants [BD=14; CTL=23]); and 8) participation in other studies that used a similar fMRI battery.

The BD group additionally had to: 1) meet DSM-IV-TR criteria for BD type I, II or NOS based on semi-structured interview (see below); 2) be engaged in or willing to commence specialty psychiatric treatment for BD; 3) able to engage in research, as defined by Clinical Global Improvement (CGI)-Severity ≤ 5 and/or Clinical Global Assessment Scale (CGAS) ≥ 50 .

The Healthy Control (CTL) group additionally had to: 1) be negative for lifetime mood or anxiety disorder, or any current psychiatric diagnosis; 2) not currently taking any medications other than over-the-counter analgesics and/or contraceptives.

A total of 64 adolescents/young adults were included in the larger study (BD N=35, CTL N=29). Participants eligible for neuroimaging were selected for the fMRI assessment; 42 participants completed the neuroimaging task for the present study (BD N=16; CTL N=26). One BD participant was excluded due to missing actigraphy data, and one control for excessive movement ($> 30\%$ of TRs with either incremental movement > 5 mm or rotation > 1 mm).

Assessment Procedures

Present and lifetime DSM-IV psychiatric and sleep disorders were ascertained by trained clinicians. Psychiatric disorders were assessed using the semi-structured Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL³³) interview along with the Mania Rating Scale and Depression Rating Scale modules. Inter-rater reliability for presence/absence of Axis I disorders on the K-SADS-PL was good ($\kappa = 0.80$). Additionally, a locally-developed Structured Clinical Interview for DSM-IV Sleep Disorders assessed sleep disorders. The Mood and Feelings Questionnaire (MFQ;³⁴) assessed depressive symptoms in the past 2-weeks, the Child Mania Rating Scale (CMRS;³⁵) assessed mania symptom severity, and the Pittsburgh Sleep Quality Index (PSQI;³⁶) assessed past-month sleep quality. Medication names and dosages were also recorded.

Prospective Sleep Monitoring

Participants completed daily sleep monitoring with actigraphy for 7-14 days prior to neuroimaging. Groups did not differ in the number of days actigraphy completed (BD= 10.53 ± 1.72 vs. CTL= 9.84 ± 1.59 , $t_{39} = 1.29$, $p = 0.205$). Participants wore an Actiwatch 2 (Phillips Respironics, Murrysville, PA) on the wrist of their non-dominant hand. The wristwatch-sized device records the number of movements per minute and stores the data in memory, yielding objective information regarding sleep patterns. Actigraphy is a gold-standard objective sleep measurement method, and reliably detects sleep in adolescents as compared with polysomnography³⁷. Average and day-to-day variability (intra-individual standard deviation) in sleep duration were derived from actigraphy. Sleep duration variability was log transformed to achieve a normal distribution.

Neuroimaging

Multi-Source Interference fMRI Task (MSIT)—The MSIT is an approximately 9-minute block-design fMRI task that reliably engages cognitive control neural circuitry^{38, 39}. The version used herein involves processing conflictual information (like the Stroop task), receiving negative feedback, and making time-pressured responses to uncontrollable stimuli that elicit subjective distress³⁸. Participants are presented with a set of three numbers (0, 1, 2, or 3), and are instructed to report via button-press the location of the number that is different. In congruent trials, the target number (1, 2, or 3) matches its position on the button press (e.g., ‘1’ always appears in the first (leftmost) position); these trials are always 100, 020, or 003. In incongruent trials, the target (1, 2, or 3) never matches its position on the button press, and the distractors are potential targets (e.g., 233; correct answer is press the second button). Accuracy feedback is given on each trial (white Ss and red Xs, or red “Too Slow”). Four blocks of incongruent trials alternated with blocks of congruent trials; each presented for 60sec with 10sec interleaved fixation cross hairs. The incongruent condition was performance-titrated, such that task accuracy was maintained around 60% on average within and between participants by speeding up inter-trial intervals. The number of trials in the subsequent congruent condition block was yoked to the number completed in the preceding incongruent block, and the inter-trial interval set to the average from the preceding incongruent block. Thus, task engagement and motor performance for both conditions were controlled across blocks and across participants. Analyses focused on a contrast of incongruent vs. congruent blocks (incongruent-congruent).

Data Acquisition and Preprocessing—MRI data were collected using a 3.0T Siemens scanner. Visual stimuli were presented by projecting images onto a rear projection screen at the participant's chest and viewed through a mirror attached to the head coil. Stimulus presentation and response registration were controlled by a Windows-based computer running E-prime (Psychology Software Tools, Pittsburgh, PA). Thirty-nine axial slices (3.2 mm isotropic voxels) per trial were acquired every 2 seconds parallel to the AC-PC line using a T2* weighted reverse spiral pulse sequence (TR=2000ms, TE=25ms, FOV=192*256mm, flip=90). Anatomical scans were acquired at the same locations as the functional imaging scans, using a standard T1-weighted pulse sequence. High-resolution MPRAGE structural scans were also collected. Analysis of Functional NeuroImaging (AFNI Version 16.0.06 software (<https://afni.nimh.nih.gov/afni>) was used to preprocess and analyze fMRI data. Preprocessing involved realignment, coregistration, segmentation, normalization into a standard stereotactic space (Colin 27; <http://www.bic.mni.mcgill.ca/ServicesAtlases/Colin27>), temporal smoothing using a 4 point Gaussian filter, and spatial smoothing using a Gaussian kernel (FWHM: 6 mm).

Procedures

At the initial clinical assessment appointment, assent/consent was obtained. Diagnostic clinical interviews were then completed with participants and a parent (parent interviews required for participants <18yr, and were optional for participants ≥18yr). The K-SADS-PL assessed psychiatric diagnoses and the Structured Interview for DSM-IV Sleep Disorders assessed sleep disorders. Participants completed mood (MFQ, CMRS) and sleep (PSQI) questionnaires, among other clinical rating measures. Eligible participants then completed

7-14 days of daily sleep monitoring with actigraphy prior to the neuroimaging assessment. At the neuroimaging assessment, participants completed fMRI task training and a mock scan in an fMRI simulator, followed by an fMRI scan which always took place in the late afternoon.

Preliminary Analyses

The BD and CTL groups were compared on demographic, clinical, and sleep variables, as well as MSIT accuracy and performance. Performance accuracy on the MSIT was computed as the percentage of trials correctly completed for each the incongruent and congruent trials. Average reaction time (RT) across correct incongruent and congruent trials was also computed. For these analyses, t-tests, chi-square tests, or fisher's exact test were used, as appropriate.

Main fMRI Analyses

At the first level analysis, individual whole brain statistical maps were computed to evaluate the MSIT incongruent-congruent contrast. TRs with extreme motion were censored if absolute motion exceeded 5mm and/or incremental motion exceeded 1mm, and motion parameters were included as covariates of no interest. All participants had <20% of TRs censored except for the aforementioned excluded CTL participant.

Second level random-effects analyses were conducted using four fronto-limbic regions of interest (ROIs) involved in cognitive control in emotional, non-emotional, and stressful contexts^{1, 40, 41}. An ROI-based approach was used because we had strong region-based hypotheses for group- and sleep-related effects based on prior BD and sleep neuroimaging studies²⁷. The anterior cingulate cortex (ACC; Brodmann Areas 24 and 32), DLPFC (Brodmann Areas 9 and 46), and VLPFC (Brodmann Area 47) were included as key regions supporting attentional control²⁴ and attentional control of emotion⁴². The bilateral amygdalae (Automated Anatomic Labeling atlas) were included as a representative subcortical region involved in emotion processing¹. These anatomical definitions were based on prior work⁴⁰. Within each ROI, voxelwise independent sample tests of incongruent-congruent BOLD response were performed using AFNI's 3dttest++. 3dttest++ examined independent sample effects of group status (BD vs CTL) as well as group*sleep interactions. Interaction effects captured group differences in the associations of sleep duration (average sleep duration) and its variability (intra-individual standard deviation of sleep duration) with BOLD response. ROI analyses used a Bonferroni-corrected voxelwise threshold of $p < 0.0125$ ($p = .05/4$) with a cluster-level correction threshold of $p < 0.05$ to correct for family-wise error. The 3dttest++ clustsim option applies a permutation approach from which cluster size thresholds are determined⁴³.

Mean parameter estimates were extracted from clusters displaying a significant effect of group or group*sleep interactions on brain activation in AFNI. These parameter estimates were imported into SPSS for post-hoc simple slope analyses of significant group*sleep interaction effects. Simple slopes were computed using the SPSS PROCESS macro⁴⁴.

Exploratory Analyses

Using the extracted fMRI data previously described, exploratory analyses included: (1) regressions paralleling the main analyses adjusted for age, sex, depressive symptoms (MFQ) and manic symptoms (CMRS); (2) correlations with medication strength in the BD group, using an approach developed for neuroimaging research⁴⁵(see Methods Supplement); and (3) correlation analyses with performance on the MSIT in both groups. Because accuracy was held consistent between incongruent MSIT blocks and congruent trial response intervals were set to the average RT for the preceding incongruent block, RT to incongruent trials was used to index behavioral performance. Statistical significance was set at $p < 0.05$.

Finally, exploratory whole-brain activity to incongruent-congruent were conducted to examine the extent to which patterns of whole-brain activity to this stimulus contrast were similar to activity patterns in our a priori ROIs (voxelwise threshold of $p < 0.005$, cluster-level threshold of $k = 20$; ⁴⁶). As in the main analyses, 3dttest++ tested the effects of group (BD vs. CTL) and within-group effects of sleep duration average and variability on BOLD activity.

Results

Demographic, Clinical, and Sleep Data

The two groups did not significantly differ on sociodemographic features (Table 1). BD had greater depressive symptoms (MFQ) and manic symptoms (CMRS) than CTL (all p 's $< .05$). The two groups did not significantly differ on sleep quality (PSQI) and sleep duration variability, but sleep duration was longer in BD than CTL ($p < .05$).

MSIT Behavioral Data

Table 2 describes MSIT behavioral results. Across all participants, mean accuracy was ~56% for the incongruent condition and ~91% for the congruent condition. As expected, incongruent condition accuracy was significantly lower than congruent condition accuracy, $t_{29} = 30.2$, $p < 0.001$, and groups did not differ in accuracy (all p values > 0.1). BD had a smaller number of trials and slower correct trial RT for both trial types ($p < .005$) than CTL, reflecting poorer task performance.

Main fMRI Analyses

Table 3 summarizes fMRI findings. There was a significant group effect on right amygdala activation ($k = 10$; peak voxel $MNI_{xyz} = 37, 1, -23$; $p < .05$) (Figure 1A and 1B). Group differences were not observed in the other ROIs. A significant group*average sleep duration interaction was observed for rostroventral ACC activation (rvACC; $k = 110$; peak voxel $MNI_{xyz} = 2, 54, 0$; $p < .01$) (Figure 2A-B). In post-hoc simple linear slope analyses, average sleep duration was positively related to rvACC activity in CTL ($b = 0.003$, $p = .002$), but not related in BD ($b = -0.001$, $p = .203$). While there was not a significant linear association between sleep duration and rvACC activity in the BD group (Figure S1), an additional regression within BD revealed a significant quadratic effect ($b = -.019$, $p = .025$) such that shorter and longer sleep duration were related to greater activation (Figure 2B). Additionally, a significant group*sleep duration variability interaction was observed in the dACC ($k = 51$; peak voxel $MNI_{xyz} = 2, 50, 5$; $p < .05$) (Table 3, Figure 2A-B). In post-hoc

simple slope analyses, sleep duration variability was negatively related to dACC activity in BD ($b=-0.71$, $p=.011$), but unrelated in CTL ($b=0.42$, $p=.133$).

Exploratory Analyses: Adjusting for Covariates

Adjusting for additional covariates did not substantially alter the main findings. For amygdala activation, after adjusting for age, sex, sleep, depression symptoms and manic symptoms there was still an effect of group status ($F(1,36)=20.77$, $p<.001$, $\eta^2=.33$) such that activation was greater in BD than CTL. Similarly, after adjusting for all covariates, there was still a group* average sleep duration interaction for rvACC activation ($b=-0.005$, $p=.004$). In post-hoc simple slope analyses, average sleep duration remained positively related to rvACC activity in CTL ($b=0.003$, $p=.024$), but only a trend in the BD ($b=-0.002$, $p=.075$). The significant quadratic effect within the BD group remained ($b=-.003$, $p=.019$). For dACC activation, the group* sleep duration variability interaction ($b=-0.92$, $p=.001$) remained after adjusting for covariates. In post-hoc simple slopes analyses, sleep duration variability was negatively related to dACC activity in BD ($b=-0.51$, $p=.013$), and now positively associated with dACC activity in CTL ($b=0.41$, $p=.026$). Older age also predicted greater dACC activation ($b=0.03$, $p=.012$).

Exploratory Correlations: Medication

In BD, medication strength composite score was not significantly related (all p -values > 0.1) to either sleep duration parameter (average and variability) or the extracted fMRI parameter estimates (amygdala, dACC, rvACC).

Exploratory Correlations: MSIT performance

Across all participants, dACC activity correlated with RT for correct incongruent trials ($r=-0.38$, $p=.014$) but rvACC activity was not ($r=-.28$, $p=.080$).

Exploratory Whole-Brain Analyses

Exploratory whole-brain analyses revealed some patterns of activity similar to those reported in the ROI analyses, such as a group*average sleep duration interaction in the rvACC, as well as additional findings (Table S1; Fig. S1).

Discussion

To our knowledge, this study provides the first report of brain activation during cognitive control under stressful conditions in transitional age youth with and without BD, and the contribution of sleep to within-group inter-individual variation in brain activation. BD youth exhibited greater amygdala activation than healthy youth during cognitive control. Additionally, sleep duration and variability differentially modulated ACC response between groups. Shorter sleep duration predicted rvACC deactivation within the healthy group, but exhibited a quadratic relationship in BD. Greater sleep duration variability predicted lower dACC engagement in BD, but not in healthy youth. Sleep patterns could contribute to inter-individual variation in cingulate sub-regions supporting cognitive control, but the directionality of these relationships may differ between psychiatrically healthy youth versus those with BD.

Our first hypothesis that BD would display altered activation in ventral prefrontal regions and the amygdala was partially supported. The amygdala was activated in BD, but deactivated in healthy youth. The latter is consistent with prior MSIT reports in healthy adults³⁸. In BD, this pattern aligns with meta-analytic findings of increased limbic response in pediatric BD² and theoretical frameworks highlighting limbic hyper-activation during cognitive processing in BD¹. As both groups found the task to be moderately stressful (BD=3.38, CTL=3.33, on a scale of 1-“Not at all” to 5-“Extremely”), this could be interpreted as a hyper-limbic response to stress in BD youth. Few studies have examined brain responses under stressful conditions in BD. One study observed blunted amygdala activation to reward anticipation during stress (vs. no stress)⁴⁷, which stands in contrast with the present findings. Amygdala activation was not related to performance. In contrast to the few other studies reporting differences in ventral PFC activation during cognitive control in pediatric BD^{48,18}, ventral PFC activation did not differ between groups. However, we may have been unable to detect differences in brain activation of small effect size for several reasons, such as a small sample or a combination of residual mood symptoms, psychiatric comorbidity, and medication use in the BD group. Another possibility is that PFC activation differences between healthy and BD youth could arise from factors other than diagnosis, such as sleep patterns.

Our second hypothesis that sleep duration average and variability would contribute to within-group inter-individual variation in BOLD response was partially supported. While sleep was not related to altered lateral PFC activation, associations between sleep duration and variability were observed in the cingulate cortex. Shorter sleep duration predicted greater rvACC deactivation in healthy youth, whereas a quadratic relationship was observed in BD. Increased rvACC engagement is hypothesized to support cognitive control in emotional contexts^{9, 49}. Though rvACC activation was unrelated to MSIT performance, the association between shorter sleep duration and rvACC deactivation in healthy youth may be unfavorable. The quadratic relationship between rvACC activation in BD could indicate differing significance of long sleep in BD versus healthy youth. While longer sleep duration (9-10hr) may be beneficial for cognitive control in healthy youth, long sleep duration may be reflective of depressogenic processes in BD. Indeed, actigraphy-derived sleep duration was longer in BD relative to healthy youth, and depressive symptoms positively correlated with sleep duration in BD only ($r=0.58$, $p=.029$).

In addition, greater sleep duration variability predicted lower dACC activity in BD, but this association was not significant in controls. Activity within the dACC region related to sleep duration variability in BD was also associated with MSIT performance (as indexed by incongruent trial RT), suggesting the relevance this region for behavior. This could indicate greater vulnerability of the cognitive control circuitry supporting behavioral performance to variable sleep patterns in BD. Such an interpretation would be consistent with rhythm instability models of BD²⁶. Sleep effects on the brain have predominantly been examined using experimental sleep deprivation studies in healthy young adults²⁸. An important implication of this finding in BD is that sleep patterns *other than* sleep loss are relevant to brain function in psychiatric samples. In exploratory analyses adjusting for additional covariates, a positive association between dACC activation and sleep duration variability emerged in healthy youth, and older age predicted greater dACC activation. Developmental

MSIT studies demonstrate increasing interference-related dACC activation from adolescence into adulthood⁵⁰, consistent with our age-related finding.

The present results should be interpreted in light of certain strengths and limitations. This study is among the first to integrate actigraphic sleep measurement with fMRI in BD (see also³⁰) and the first to our knowledge in a sample of transitional age youth. Moreover, while many studies have employed emotional and non-emotional variants of the Stroop task to probe cognitive control circuitry in BD^{13, 18}, the present study incorporates a novel application of a stressful cognitive control task. We observed effects of BD diagnosis and sleep in brain regions implicated in cognitive control in emotional¹ and stressful contexts⁴¹. Akin to other studies of pediatric BD^{18, 48, 51}, limitations here include a small sample size, a range of clinical symptoms, and psychotropic medication use. Though significant medication effects were not detected in exploratory analyses, medications can have a normalizing effect on brain circuitry⁵² and may mitigate the ability to detect group differences. In addition, the inclusion of BD-NOS diagnoses adds a significant degree of variability to classic conceptualizations of mania. Finally, this study was correlational in nature. Future studies with longitudinal designs or experimental sleep manipulation would clarify causal relationships observed between sleep and brain function.

In transitional age youth with BD, sleep patterns may be an important contributor to inter-individual variation in activation within cingulate regions supporting cognitive control under stress. Interventions designed to stabilize sleep patterns may have the potential to normalize cognitive control-related ACC activations in BD, which may be key for regulating hyperlimbic responses characteristic of the disorder. Additional work investigating the relevance of sleep patterns to brain function and psychiatric status in BD is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Pittsburgh Foundation (Franzen; Goldstein), NIMH grant K01MH111953 (Soehner), NIDA grant R01DA033064 (Franzen) and NIH grant UL1TR000005. This study was presented as an abstract at the 71st Annual Society of Biological Psychiatry Convention, Atlanta, GA, May 12-14, 2016 and the 60th Annual SLEEP Meeting, Denver, CO, June 11-15, 2016.

Funding Sources: This research was supported by the Pittsburgh Foundation (Franzen; Goldstein), NIMH grant K01MH111953 (Soehner), NIDA grant R01DA033064 (Franzen) and NIH grant UL1TR000005.

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Figure 1. (A) Significant group effect on right amygdala activation to the incongruent-congruent contrast ($k=10$; peak voxel $MNI_{xyz}=37, 1, -23$; $p<.05$), and (B) plotted by group status.

Figure 2.

(A) Significant group*average sleep duration interaction on bilateral rACC activation to the incongruent-congruent contrast (rvACC; $k=110$; peak voxel $MNI_{xyz}=1, 36, 28$; $p<.02$), and (B) extracted rvACC activation estimates plotted versus average sleep duration by group. Trend lines indicate a simple linear slope in CTL and a quadratic slope for BD group. BD=Bipolar Disorder; CTL=Control.

Figure 3.

(A) Significant group*average sleep duration variability interaction for bilateral dACC activation to the incongruent-congruent contrast (dACC; $k=51$; peak voxel $MNI_{xyz}=2, 29, 41$; $p<.05$), and (B) extracted dACC activation estimates plotted versus natural log-transformed sleep duration variability by group. Trend lines indicate simple linear slopes in BD and CTL. BD=Bipolar Disorder; CTL=Control.

Table 1

Demographic, clinical, and sleep characteristics, by group status.

<i>Demographic & Clinical</i>	BD (N=15)	CTL (N=25)	<i>Statistic</i>	<i>p</i>
	<i>Mean (SD) or N (%)</i>	<i>Mean (SD) or N (%)</i>		
Age (years)	18.14 (2.74)	19.47 (2.68)	$t_{38}=1.51$	0.139
Sex (% female)	11 (73.3%)	17 (68.0%)	++	1.000
White/Caucasian (%)	12 (80.0%)	17 (68.0%)	++	0.486
SES (Hollingshead)	2.68 (1.37)	3.43 (1.57)	$t_{37}=1.64$	0.117
MFQ Score	17.29 (19.09)	4.42 (5.02)	$t_{36}=2.47$	0.002
MFQ Severity Ratings			$X^2=7.66$	0.022
Mild (<20)	10 (71.4%)	24 (100%)		
Moderate (20-34)	2 (14.3%)	0 (0%)		
Severe (>34)	2 (14.3%)	0 (0%)		
CMRS Score	14.31 (13.68)	4.75 (5.21)	$t_{35}=2.42$	0.005
Any Comorbid Axis 1 Disorder	11 (73.3%)	--	--	--
Anxiety Disorders	4 (26.7%)	--	--	--
ADHD	8 (53.3%)	--	--	--
Disruptive Behavior Disorder	1 (6.7%)	--	--	--
BD Subtype				
Type I	4 (26.7%)	--	--	--
Type II	5 (33.3%)	--	--	--
NOS	6 (40.0%)	--	--	--
BD Age Of Onset (Yrs)	11.07 (3.73)			
Psychotropic Medication	15 (100%)	--	--	--
Number of Medications	3.33 (1.98)	--	--	--
Medication Dosage Strength	3.80 (2.24)			
Antipsychotic	11 (73.3%)			
Antidepressant	3 (20.0%)			
Mood Stabilizer	11 (73.3%)	--	--	--
Stimulant	4 (26.7%)			
Sedative/Hypnotic	1 (6.7%)	--	--	--
Pittsburgh Sleep Quality Index Global Score	6.85 (3.08)	5.75 (4.57)	$t_{36}=0.80$	ns
Average Sleep Duration (minutes)	428.3 (73.7)	369.6 (43.4)	$t_{38}=3.18$	.011
Sleep Duration Variability (minutes)	10.5 (1.7)	9.8 (1.5)	$t_{38}=0.69$	ns

Note. BD=Bipolar Disorder; CTL=Healthy Control Adolescents; SD=Standard Deviation; ++=Fisher's Exact Test; SES=socioeconomic status; MFQ=Mood and Feelings Questionnaire; CMRS=Child Mania Rating Scale; ADHD=Attention-Deficit Hyperactivity Disorder

Table 2

Multi-source interference task behavioral performance, by group status.

	BD (N=15)	CTL (N=25)	<i>Statistic</i>	<i>p</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>		
Number Incongruent Trials	122.07 (6.41)	131.92 (8.70)	$t_{38} = 4.10$	<.001
Number Congruent Trials	122.07 (6.41)	131.92 (8.70)	$t_{38} = 4.10$	<.001
Accuracy Incongruent Trials (%)	56.33 (8.84)	56.66 (3.92)	$t_{38} = 0.14$	0.891
Accuracy Congruent Trials (%)	91.71 (3.35)	90.71 (6.99)	$t_{38} = -0.61$	0.548
Reaction Time Incongruent Trials (msec)	710.78 (128.73)	584.75 (126.96)	$t_{38} = -3.01$	0.005
Reaction Time Congruent Trials (msec)	477.18 (61.10)	419.60 (42.89)	$t_{38} = -3.21$	0.004

Note. BD=Bipolar Disorder; CTL=Healthy Control Adolescents; SD=Standard Deviation.

ROI analyses of group, average sleep duration and sleep duration variability on BOLD activation to incongruent-congruent

Table 3

Comparison	Region	Slope	BA	Side	k	MNI Coordinates				p
						x	y	z		
Group Effect	Amygdala	+	--	R	10	37	1	-23		<.05
Group*Average Sleep Duration Effect	rvACC	-	24,32	L, R	110	1	36	28		<.02
Group*Sleep Duration Variability Effect	dACC	-	9,32	L, R	45	2	29	41		<.05

Note. ROI=region of interest; BOLD=blood oxygen level dependent; BA= Brodmann Area; -- indicates data not applicable; L=left; R=right; rvACC=rostroventral anterior cingulate cortex; dACC=dorsal anterior cingulate cortex; k=cluster size in voxels