UPMC LIFE CHANGING MEDICINE

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Jair Soares, MD, PhD
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Dear Dr. Soares,

We are grateful for this opportunity to submit a revision for MS# JAD_2015_1138 "Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder". We have carefully revised the paper in accordance with the very helpful feedback we received from the reviewers. The changes made to the manuscript are detailed below.

Reviewer #1

This is a very well written paper, with sound methodology and objective interpretation of the results. I commend the authors for their work and would like to suggest few changes to improve the quality of their paper.

1. I commend the authors for choosing the PSQI as it has good external validity. However, given evidence of potential discrepancies between subjective and objective measures of sleep duration and impact of mood on the self-report of sleep duration (see R. Gonzalez, C. Tamminga, M. Tohen, T. Suppes, Comparison of objective and subjective assessments of sleep time in subjects with bipolar disorder, Journal of Affective Disorders, Volume 149, Issues 1–3, July 2013, Pages 363-366), I was wondering how the researchers interpret this evidence, and how they interpret it in relation to the current findings.

This is a valid concern when using self-reported sleep data in psychiatric samples. In the discussion, we alluded to the limitation that psychiatric samples can provide less reliable self-report estimates of sleep (Bliwise et al., 1993), but have clarified this point and now reference Gonzalez et al. (2013), on page 20 with the following – additions are highlighted.

"Some evidence suggests that psychiatric samples can provide less reliable self-report estimates of sleep in comparison with objective estimates (Bliwise et al., 1993; Gonzalez et al., 2013)."

Of note, in the present study, approximately half of the sample was unaffected by psychopathology. Thus, while it is possible current symptoms affected self-report estimates of sleep in some youth, the neuroimaging findings remained in the subsample unaffected by psychopathology. Nonetheless, future studies would certainly benefit from incorporating both self-report (diary, questionnaire) and objective (actigraphy) estimates of sleep.

2. Could the authors provide additional references to support their statement that reduced sleep is part of mania (besides the APA reference).

We have now included a reference to Harvey (2008) on page 4, paragraph 2. This review article reports that reduced sleep need is observed in 69-99% of manic episodes in patients with bipolar disorder.

Harvey, A.G. 2008. Sleep and circadian rhythms in bipolar disorder: Seeking synchrony, harmony, and regulation. Am J Psychiatry 165:820-829.

3. Could the authors provide some information linking sleep, self-rating of sleep duration, and mood (self-rated or externally assessed in mood disorders) in their introduction. It could help better understand the bigger picture.

We have now incorporated references highlighting links between self-rated sleep duration and mood disturbance in the Introduction (pg. 4 paragraph 2):

"Links between shortened sleep duration and mood disturbance has also been observed in community samples and across affective disorders more broadly (e.g., Barnes & Meldrum, 2015; Nixon et al., 2008; Raniti et al., 2016; Sivertson et al., 2014; Zohar et al., 2005;)."

4. Why did the authors select self-reports rather than a mix of self-reports and clinician administered mood assessments?

We restricted our analyses to rating measures collected on the day of scan for temporal synchrony and methodological consistency with previous publications in this sample (Manelis et al., 2015; Manelis et al., 2016). Clinician-rated assessments were collected on the day of the clinical evaluation, which preceded the scan. However, we have now included the absence of scan-day clinician-rated mood assessments as a limitation in the discussion section (pg. 21, paragraph 1).

"Clinician-rated mood assessments were not conducted on scan day. Future research would benefit from incorporating clinician-rated mood assessments with parent- and self-report."

5. Page 10: could the authors explain why the order of trials of guessing blocks had a predetermined outcome order?

This validated block design reward task is standardized with predetermined outcomes for consistency across participants. This is important given the relatively short duration (6 minutes) of the task.

6. Page 13. Could the authors clarify if the voxelwise regressions relative the win>control comparison were conducted in regions that were active in both OBP and OCP during this contrast or only in the OBP. Also did they focus on regions previously shown to be active in the literature or all the active regions?

Thank you for the opportunity to clarify. For the main analyses, the anatomical region of interest mask of key reward related circuitry (e.g., Liu et al., 2011) was constructed using the WFU PickAtlas (see pg. 11, paragraph 3). On an exploratory basis, we examined all regions engaged by the task in whole-brain analyses (see pg. 17, paragraph 2 and Supplement).

7. Page 16: I would recommend that the authors describe at a very minimum in 1-2 sentences what the "exploratory whole brain analyses" results were all about. A reference to the supplementary table 1 is not sufficient.

In the Exploratory Analysis section (pg. 13, paragraph 3) we now describe the purpose of the whole-brain analyses:

"Lastly, we conducted exploratory whole-brain activity and VS connectivity to win-control to examine the extent to which patterns of whole-brain activity to this stimulus contrast was similar to activity and connectivity pattern in our a priori ROI masks (voxelwise threshold of $p < 0.005$, cluster-level threshold of k=20) (Lieberman and Cunningham, 2009)."

We have also have elaborated on this point in the Results section (pg. 17 paragraph 2):

"Exploratory whole-brain regressions revealed patterns of activity and VS connectivity similar to those reported in the ROI analyses, as well as additional findings (See Supplemental Table 2)."

8. Typo page 13: "were assesses" should be "were assessed"

This typographical error has been fixed.

Reviewer #2

This is a well written paper with a unique set of offspring of parents with BD (OBP) and offspring of parents with non-BD psychopathology (OCP). The focus is on sleep duration, mood dysregulation, and reward circuitry function. Overall, this is an important topic of investigation. There are some concerns, however, that should be addressed:

1. The title of the study should also include "mood dysregulation" since this is one of the main variables examined in the investigation.

Thank you for this suggestion. The title has been amended to: "Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder."

2. The total sample included 70 offspring (OBP = 35; OCP = 35). Given that participants were excluded for various reasons the analyses were conducted on fewer participants (OBP = 25; OCP = 21). Where there any significant differences between these two groups initial sample vs. sample included in the analyses?

Of the 70 offspring (OBP=35; OCP=35) who completed neuroimaging, 63 met inclusion criteria for this study (OBP=34; OCP=29). A total of 17 offspring were not included in the analyses due to an inability to complete the functional tasks in the fMRI scanner either due to scheduling limitations, participant cooperation, or scanner malfunction; excessive motion (>4mm) during the fMRI task; and missing sleep data. A comparison of the 17 excluded offspring and the 46 included offspring along sociodemographic, sleep, and clinical characteristics is now included in Supplemental Table 1 and discussed in the Supplemental Analysis section (Paragraph 1).

3. Information has to be provided regarding the mood state of the parents at the time of completion of the MFQ-P and SCARED-P. It is not clear whether parental mood state played a significant role. Research shows that parental evaluations of their children's behavior are influenced by their own mental state, therefore raising questions about the validity of parent-report measures by parents with mental illness. This point should be better integrated in this study.

The reviewer raises an important point. Parental mood has been shown to affect ratings of offspring mood, and we have now included this limitation in the limitations section (pg. 21, paragraph 1; see highlighted section below). However, a prior report from the BIOS sample

observed that patterns of findings related to mood in OCP and OBP remained even after adjusting for current parental mood episodes (e.g., Birmaher et al., 2013). Moreover, in the present study, parent report of the MFQ and SCARED scores *did not* significantly differ between groups, while measures of mood dysregulation (CALS, PGBI-10M) did differ between groups.

"Mood assessments included in the present study were parent-reported, which can be affected by parental mood at the time of rating (e.g., Birmaher et al., 2013). Clinician-rated mood assessments were not conducted on scan day. Future research would benefit from incorporating clinician-rated mood assessments with parent- and self-report."

4. Better justification should be provided for conducting Exploratory analyses (i.e., reasons for examining medication use given prior literature and standard in the field, significance etc.). This justification should be included in the Introduction section as well.

We have provided additional justification for pursuing exploratory analyses examining the consistency of the primary findings within the medication- and psychopathology-free subsamples. This issue is now addressed in the Exploratory Analysis section (pg. 13, paragraph 2; additions highlighted below).

"Psychiatric medication use (e.g., Phillips et al., 2008) and current psychopathology (e.g., Whitton et al., 2014) have been shown to affect neuroimaging findings. Thus, we followed a prior method (Manelis et al., 2015) to test the effects of medication use and current diagnosis on the neural activity and functional connectivity identified in the primary analysis."

5. There are a very large number of analyses conducted with a small sample size in this study. This represents a significant concern. What are the statistical considerations here regarding the small sample size, large number of analyses, power, etc? It is understandable, however, that as a first study in this area the authors are trying to use the data and pursue relevant analyses. This weakness can be remediated by including a short write-up in the analyses section to address the concern and again in the limitation section. Also, to reflect this point the study title will be more accurate, if revised to "Preliminary investigation of the relationships…"

Thank you for these recommendations. First, we have amended the study title to reflect that this is a preliminary investigation, "Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder". Second, we make note of the relatively small sample size, large number of analyses, and statistical power as considerations in Discussion section (pg. 20, paragraph 2).

"The relatively small sample size affects statistical power, and may have limited our ability to detect weaker interaction effects. There were also a large number of analyses. Findings should be replicated in a larger sample."

We also highlight the fact that our main analyses comprised analyses of the main effect of group and group x sleep duration interaction in only two parallel regression models in SPM, focusing on activity and functional connectivity, and relationships with mood symptoms. Other analyses were exploratory.

6. The results should be linked to the study hypotheses. For each results section, the authors should include a statement linking the original hypotheses to the specific results (i.e., "Consistent with the hypothesis …. , we found …. " or "Contrary to the hypothesis…, we found…"). Also, the discussion of results in the Discussion section should be framed similarly and the link to the original hypotheses has to be reestablished clearly for the reader. This will contribute to greater clarity of the manuscript.

The results have been linked to study hypotheses throughout the Results and Discussion sections.

7. The paragraph beginning with "The left lateralization of the observed…." in the Discussion section (page 19) should be expanded by providing more clarification on what might be contributing to the present study yielding different findings from previous studies such as Singh et al., 2014 and Manelis et al., 2016.

We have added an interpretation for the laterality of the connectivity findings, and speculation about the implications (pg. 20, paragraph 2; additions in highlighted section below):

"The left lateralization of the observed striatal connectivity patterns is intriguing, given a growing number of studies reporting increased left VLPFC activation during reward processing in adult BD (for review see Phillips and Swartz, 2014; Nusslock et al., 2014), and are consistent with theories proposing a role of the left prefrontal cortex in encoding approach-related emotions (Pizzagalli et al., 2005). However, the present findings stand in contrast to prior work in OBP observing altered right VLPFC connectivity with pregenual cingulate gyrus (Singh et al., 2014) and bilateral VS (Manelis et al., In Press) during reward processing. The right VLPFC has been interpreted as serving an emotion regulatory function during reward processing (Singh et al., 2014; Manelis et al., 2016). Herein, given that sleep duration was differentially related to VS connectivity with the left anterior insula/VLPFC region, this could reflect a role of sleep duration in the modulation of encoding salient, approach-related emotions during reward processing."

8. There is only one brief sentence in the Discussion section making a recommendation for future research. This is not sufficient. The authors should elaborate more on the relevance of the study findings for future research and make recommendations for future studies. What are some of the research questions that remain unanswered based on the present study findings? What could be a next step that builds on the present findings? How could the present findings be used to generate novel hypotheses and research questions with relevance to understanding neurobehavioral risk pathways or research questions with direct clinical relevance, and other? What are the implications for future studies examining this subject in OBP?

We have elaborated on future directions in the Discussion section (pg. 21):

Future research designed to establish causal relationships among sleep, reward circuitry function, and mood dysregulation in at-risk youth is recommended. While reciprocal relationships among these phenomena likely exist, understanding the neurobehavioral pathways linking sleep to the initial emergence of mood dysregulation could provide opportunities for preventative sleep-focused treatments, and identify neural markers to serve as clinical outcomes. Longitudinal research is necessary to establish the hypothesized temporal patterns, particularly whether neuroimaging markers mediate relationships between sleep and mood dysregulation. Experimental manipulations of sleep would also hold great utility for establishing causal links. For example, sleep extension paradigms could be used to ascertain whether brain function and mood dysregulation are improved in high-risk youth with insufficient sleep.

While the focus in the present study was on sleep duration, it is also possible that other sleep parameters are relevant to the onset and course of BD. For example, instability of sleep-wake patterns is also common in BD (e.g., Ng et al., 2014), and a target of existing psychosocial interventions such as Interpersonal and Social Rhythm Therapy. Thus, future studies would benefit from a more comprehensive assessment of sleep, examining a wider set of sleep parameters using both objective and subjective measures.

9. The last paragraph of the Discussion states "These findings, and future work in the BIOS samples, could provide neurobehavioral targets to guide preventive treatments in

OBP." The authors should elaborate on whether and how the findings from this study could be useful with respect to the development of early intervention and prevention approaches for OBP. More needs to be written to address this concern and to highlight the significance and importance of the current findings and potential implications for clinical treatment etc. Also, based on the present findings, what are the implications for clinicians treating OBD and their parents with BD?

We have elaborated on clinical implications in the Discussion section (pg. 21-22); please see Reviewer 2, comment 8 above.

Reviewer #3

Summary:
The authors reported the findings of the associations between sleep duration and reward circuitry network in youth offspring of parents with bipolar disorder (OBP). They showed that altered reward-related ventral striatum-insula connectivity could represent a neural pathway for the development of mood dysregulation in OBP, and may be modulated by reduced sleep duration. Overall, the finding seems sound and it may be valuable to the research community of studying affective disorders. However, this reviewer requests additional information to be added for clarification.

Major Critique:
1. One of my major concerns is the conclusion statement of the study. It is clear that there is some correlation between sleep duration and mood dysregulation in OBP. However, the data did not provide enough support for the cause or consequence correlations. One may argue that mitigating mood disorder could improve the quality of sleep and duration of sleep.

Reviewer 3 brings up an important point. We have incorporated language in the Discussion section recognizing the likelihood that reciprocal relationships exist between sleep duration, brain function, and mood dysregulation and that future work is necessary to establish causality (pg. 21 paragraph 2, and last sentence of pg. 22; Please see text in response to reviewer 2, comment 8). The goal of the paper was, on a preliminary basis, to establish associations among these three phenomena. The majority of youth in this present sample have not yet developed mood disorders (only 4 of 25 OBP and 3 of 21 OCP have unipolar depression), but some are experiencing early signs of mood dysregulation. Sleep disturbance often precedes the onset of BD (e.g., Ritter et al., 2011) and its adjunctive treatment can improve clinical course in those with established BD (e.g., Harvey et al., 2015). Thus, disrupted sleep has the potential to serve as a target for preventative treatments prior to the emergence of significant and impairing signs of mood dysregulation.

2. Although the topic and the finding of this study are interesting, this reviewer has difficulty to go through this article the first time. With some assumptions and guesses, I *think* I finally got the point. But, it would be ideal to have the authors addressing these issues directly in the content so other readers do not have to go through the trouble I had.

For example, the authors have never clearly define what "group*sleep duration interactions" really is. Since this one of the major point that the authors try to deliver, it is important for the reader to know what it means in term of physiology and how the data address this point.

"Group*sleep duration interaction" is the interaction term generated for the regression equation. It is the dummy-coded group status variable (OBP = 0.5, OCP = -0.5) multiplied by mean-centered sleep duration. A significant group*sleep duration interaction within a brain region (cluster) indicates that the association between sleep duration and neuroimaging outcomes (BOLD activity

and VS connectivity) differs between groups. For example, activation in a set of voxels increases with increase in sleep duration in Group A, but decreases with increase in sleep duration in Group B.

3. It is also very annoy to find that this article has used symbol ">" in many occasions without clearly defined and may have different meanings. For example, it seems that the authors used "win>control" to represent "win versus control". But, I am not sure if "OCP>OBP" also represent "OCP versus OBP". If it is so, then I am confused what would be the difference between OCP>OBP and OBP>OCP (other than different direction) in the sentence of "Group effects were observed for right posterior insula activity (OCP>OBP) and VS-left posterior insula connectivity (OBP>OCP)." (Abstract) Please define them through the content!

In "OBP>OCP", the ">" sign is used to denote "OBP is greater than OCP" for a given dependent variable. As this is a widely accepted symbol, we have kept this terminology in the Abstract. Though there is a precedent for referring to our contrast of interest as "win>control" (e.g., Bebko et al., 2014), we have changed to "win-control" throughout the manuscript. The win-control contrast was constructed by subtracting control blocks from win blocks, so that positive activations would indicate that there was greater BOLD activity during win blocks compared to control blocks.

Minor Critique:

4. Abstract: Limitations declaration is insufficient and is not acceptable.

We do recognize that there are many limitations that merit consideration in the interpretation of study findings. We have striven to comprehensively address these issues in the Discussion, with important additions made based on reviewer feedback. Due to the space constraints in the abstract, we have included "Cross-sectional design and small sample size" as two key limitations.

5. Page 10: "echo-planar 238 sequence". Is "238" a typo? If not, what does it mean?

This was a typographical error; it was corrected to "echo-planar sequence".

6. Page 12: Since there is no clear define for "group*sleep duration interactions", it is unclear what the resultant interaction terms are.

A significant group*sleep duration interaction indicates that the slope for sleep duration differs between groups. Simple slope analyses along with plots of extracted activation and connectivity estimates were performed to depict the direction of the group-specific slopes for significant interactions.

7. Page 14: Is "(ps<.05)" a typo for "p<.05"? If not, what is this?

This was a typographical error. This as been amended to "all p-values <.05" to reflect that all statistical tests listed in the sentence were p<.05 (pg. 14, paragraph 1).

8. Table 3: Please define "k" and "t(42)" in the Note here.

These definitions have been incorporated into the Table 3 Note.

"Note. ROI=region of interest; BOLD=blood oxygen level dependent; PPI=psychophysiological interaction; BA= Brodmann Area; -- indicates data not applicable; L = left; R = right; daMCC = dorsal anterior mid-cingulate cortex; VLPFC = ventrolateral prefrontal cortex; Group status was dummy coded OBP=0.5 and OCP=-0.5; k=cluster size in voxels; t(df)."

9. Figures 1D and 2D: don't you supposed to have two R2 values, since there two regressionlines here. It is not sure why you have one each in Figures 1C and 2C.

Thank you for noticing this confusing information. Figures 1D and 2D plot extracted activation and connectivity estimates to display the direction of the group-specific slopes for significant interactions. The R^2 values are for the overall regression that includes group status, sleep duration, and group*sleep duration as predictors, thus there is only one R^2 value. Similarly, in Figures 1C and 2C, the R^2 values are for the overall regression equation. We have clarified this in the Figure 1 and 2 captions with the following highlighted information. For example:

"(D) Extracted left daMCC BOLD activity estimates plotted versus sleep duration for group*sleep duration interaction, trend lines indicate simple slopes for each group, R^2 represents variance explained for the overall regression. OBP = offspring of bipolar parents; OCP = offspring of control parents; daMCC=dorsal anterior mid-cingulate cortex."

Page 37, S1: What does it mean by "win<control contrast"? This is the only symbol "<" in the entire manuscript.

We have amended this to be win-control.

Thank you again for the thoughtful review this paper received and for the opportunity to submit this revision. We believe that the current version of the paper is a significant improvement upon the previous one. We look forward to hearing the outcome of this resubmission and would welcome further guidance for improving the manuscript.

With thanks,

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Abstract

Background: Altered reward circuitry function is observed in individuals with bipolar disorder (BD) and their unaffected offspring (OBP). While OBP are at elevated risk for BD, modifiable risk factors that may exacerbate neural vulnerabilities in OBP remain under-characterized. As sleep loss is strongly linked to mania in BD, this study tested associations between sleep duration, reward circuitry function, and mood dysregulation in OBP.

Methods: Two groups of youth unaffected with BD (9-17yr) completed a number-guessing fMRI reward paradigm: 25 OBP and 21 age-sex-IQ-matched offspring of control parents with non-BD psychopathology (OCP), to differentiate risk for BD from risk for psychopathology more broadly. Regressions tested effects of group status, self-reported past-week sleep duration, and their interaction on neural activity and bilateral ventral striatum(VS) functional connectivity to win>control. Correlations with parent-reported mood dysregulation were assessed.

Results: Group effects were observed for right posterior insula activity (OCP>OBP) and VS-left posterior insula connectivity (OBP>OCP). Group*sleep duration interactions were observed for left dorsal anterior-mid-cingulate(daMCC) activity and VS-left anterior insula/ventrolateral prefrontal cortex(VLPFC) connectivity. Specifically, sleep duration and daMCC activity were positively related in OBP, but negatively related in OCP and sleep duration and VS-left anterior insula/VLPFC connectivity were negatively related in OBP, but positively in OCP. Additionally, increased VS-left posterior insula connectivity and VS-left anterior insula/VLPFC connectivity were associated with greater mood dysregulation in OBP only.

Limitations: Cross-sectional design and small sample size.

Conclusions: Altered reward-related VS-insula connectivity could represent a neural pathway underpinning mood dysregulation in OBP, and may be modulated by shortened sleep duration.

Keywords: Bipolar disorder risk; sleep; reward processing; functional MRI

Preliminary investigation of the relationships between sleep duration, reward circuitry function, and mood dysregulation in youth offspring of parents with bipolar disorder

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Running title: sleep and reward in youth at risk for BD

Abstract

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Keywords: Bipolar disorder risk; sleep; reward processing; functional MRI

Introduction

Characterizing the neurobehavioral processes that predispose youth to bipolar disorder (BD) is vital for preventing the disorder and improving treatment outcome. Neuroimaging studies have identified functional abnormalities within neural circuitry supporting information processing domains known to be disturbed in BD, such as reward processing (Phillips and Swartz, 2014). As parental history of BD is one of the most robust risk factors for developing BD (Birmaher et al., 2009), recent neuroimaging studies have focused on examining reward-related neural circuitry in offspring of bipolar parents (OBP), and have yielded valuable insights into neural processes that may predispose to BD (Manelis et al., 2016, Singh et al., 2014). Yet, while OBP are at elevated risk for BD, many do not develop the disorder. Thus, it is necessary to begin characterizing potentially modifiable risk factors that may interact with familial risk to amplify neural vulnerability for BD. The present study focuses on sleep duration as one such risk factor, as sleep loss has been linked to both the development of mania (Plante and Winkelman, 2008) and altered reward circuitry function (Hasler et al., 2015).

Reward processing in humans is supported by a complex prefrontal-subcortical neural network (Haber and Knutson, 2010; Liu et al., 2011), which includes the ventral striatum (VS), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), ventrolateral prefrontal cortex (VLPFC), and insula. Neuroimaging studies in BD patients have observed functional abnormalities during reward processing relative to healthy controls, namely elevated neural activity within the ventromedial PFC (vmPFC), OFC, VLPFC, and VS (for review see Nusslock *et al.* 2014) and reduced negative VS-VLPFC functional connectivity (Trost et al., 2014). Two recent fMRI studies have also observed functional abnormalities during reward tasks in OBP. In one report, elevated negative bilateral VS-right VLPFC connectivity to

win and loss trials (vs. control trials) distinguished OBP from both offspring of healthy parents and offspring of parents with non-BD disorders (Manelis et al., 2016). Another study observed elevated left VLPFC activation and reduced pregenual ACC-VLPFC connectivity during reward processing in healthy OBP relative to healthy control youths (Singh et al., 2014). VS and insula activation to reward receipt were also positively related to impulsivity in OBP (Singh et al., 2014). Together, these data indicate that both BD patients and OBP exhibit elevated reward-related neural activity and altered functional connectivity among ventral prefrontal cortical-striatal regions (vmPFC, OFC, VLPFC, VS) and insula.

A separate line of work has demonstrated a key role of sleep disruption in BD (Plante and Winkelman, 2008). Disturbed sleep is a predictor of BD onset in at-risk samples (Levenson et al., 2015; Ritter et al., 2011), it is prospectively linked to worsening symptoms of mania and depression in youth with BD (Lunsford-Avery et al., 2012), and it is the top prodromal symptom of mania in adult BD (Jackson et al., 2003). Sleep *loss*, or short sleep duration, may have particular importance to the emergence of mood dysregulation characteristic of BD. Reduced sleep need is a unique (American Psychiatric Association, 2001) and highly prevalent (for review see Harvey, 2008) feature of mania, experimental sleep deprivation can trigger (hypo)mania in BD patients (e.g., Barbini et al., 1998; Colombo et al., 1999), and sleep loss predicts subsequent manic symptoms (Bauer et al., 2006). Links between shortened sleep duration and mood disturbance have also been observed in community samples and across affective disorders more broadly (e.g., Barnes and Meldrum, 2015; Nixon et al., 2008; Raniti et al., 2016; Sivertsen et al., 2014; Zohar et al., 2005).

Disturbed sleep, and sleep loss in particular, has also been tied to altered reward circuitry function in healthy samples. In healthy adolescents, correlational studies of sleep and neural

response to monetary rewards have linked shorter habitual sleep duration with decreased VS activity (Holm et al., 2009); more variable sleep timing with reduced dorsal mPFC (dmPFC)/ACC and VS activity (Hasler et al., 2012); and poorer sleep quality with increased insula activity and decreased lateral PFC-insula connectivity (Telzer et al., 2013). Adult studies using acute sleep deprivation paradigms have reported increased VS, vmPFC, and OFC activity (Mullin et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011a), and reduced dmPFC/ACC deactivation (Mullin et al., 2013), in response to monetary reward. A study examining the rewarding effects of pleasure-evoking images observed that acute sleep deprivation biased young adults toward more positive appraisals of the images, and led to elevated activity (striatum, amygdala, insula) and altered connectivity (e.g., amygdala, insula, and lateral PFC) within reward-related regions (Gujar et al., 2011). Overall, studies have associated sleep loss (or disrupted sleep) with increased reward-related neural activity and altered connectivity among ventral prefrontal cortical-striatal regions (vmPFC, OFC, VS) and insula, along with deactivation within dorsal frontal regions (dmPFC, ACC).

While there is evidence for separate effects of family history of BD and sleep loss on reward processing, research has not yet examined the interaction of these risk factors. In OBP who have not yet developed BD, sleep loss may exacerbate existing functional abnormalities in reward-related ventral prefrontal cortical-striatal regions and reduce activation within dorsal frontal regions. However, in examining this question in OBP, it is important to differentiate risk for BD from risk for psychopathology more broadly. OBP are at heightened risk of developing a range of non-BD psychiatric conditions in addition to BD (Birmaher et al., 2009). Parents with BD also have high rates of non-BD comorbid disorders (Merikangas et al., 2007). Thus, it is necessary to account for both the impact of risk for non-BD psychopathology and environmental

effects of living with parents with non-BD psychopathology when selecting a comparison offspring group. To control for these effects, we included offspring of control parents with non-BD psychiatric disorders (OCP), which included lifetime diagnoses of depression, anxiety, behavioral, and substance use disorders.

The goal of this study was thus to examine associations between sleep duration, reward circuitry function, and mood dysregulation in youth at high- and low-familial risk for BD (as a function of parental history of BD). We used a well-validated number-guessing paradigm (win, loss, and control blocks) (Bebko et al., 2014; Forbes et al., 2009) to examine reward-related neural circuitry. Sleep duration was assessed using a validated self-report questionnaire. Symptoms of mood dysregulation (e.g., mood lability, positive mood/energy dysregulation) were assessed via parent report. Two aims were evaluated. Aim 1 was to test the association between self-reported sleep duration and reward circuitry function, and the moderating effect of high- or low-familial risk for BD (as a function of parental history of BD). We hypothesized that, across all youth, shorter sleep duration would be associated with (a) reduced activity in dorsal prefrontal cortical regions implicated in reward processing (dACC, dmPFC), (b) elevated activity in ventral prefrontal cortical-striatal regions implicated in reward processing (vmPFC, OFC, VLPFC, VS) and insula, and (c) altered VS connectivity with ventral prefrontal cortical regions (VLPFC, OFC, vmPFC) and insula to win-control. Given previous findings showing similar patterns of altered reward circuitry function to those described above in OBP versus OCP (Manelis et al., 2016), we also predicted that group status would moderate sleep-reward circuitry function relationships, such that the above associations between sleep duration and reward circuitry function would be stronger in OBP than OCP. Aim 2 was to examine whether group- or sleep-related alterations in reward circuitry function were associated with mood dysregulation

symptoms (e.g., mood lability, positive mood/energy dysregulation) in OBP and OCP. We hypothesized that, within OBP, reward-related activation and connectivity patterns related to group status, sleep duration, or their interaction would be associated with elevated symptoms on these measures.

Methods

Participants

Two groups of participants (9–17 years old) *who were not affected with BD* were included in this study: (1) 25 offspring of parents with bipolar disorder type I or II (OBP) and (2) 21 age-, sex-, and IQ-matched children of parents with non-BD psychopathology (offspring of control parents; OCP). Several participants were taking psychotropic medication (OBP N=2; OCP N=3) and had non-BD psychopathology (OBP N=9; OCP N=10). Participants were recruited from the Pittsburgh Bipolar Offspring study (BIOS), an ongoing longitudinal study on the psychopathology and functioning of offspring of individuals diagnosed with BD (Birmaher et al., 2009). This study was approved by the Institutional Review Board of the University of Pittsburgh (Pittsburgh, PA, USA) and all participants provided written informed assent/consent as appropriate. Exclusion criteria for all parents included: lifetime diagnoses of schizophrenia, mental retardation, and mood disorders secondary to substance abuse, medical conditions, or medications. OCP parents were also excluded if they had first-degree relatives with BD. Offspring exclusion criteria included: systemic medical illness, neurological disorders, history of head trauma, alcohol or illicit substance use, presence of metal objects in their body, claustrophobia, IQ<70 as assessed by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), unable to read and write in English, corrected visual acuity worse than 20/40 on the

Snellen visual acuity test, and missing sleep data. The total sample included 70 offspring (OBP *N*=35; OCP *N*=35). Of these, participants were excluded due to: not meeting study inclusion criteria [lack of parental Axis I pathology in OCP (*N*=5); pervasive developmental disorder diagnosis (OCP *N*=1)]; an inability to complete the functional tasks in the fMRI scanner either due to scheduling limitations, participant cooperation, or scanner malfunction (OBP *N*=6; OCP *N*=5); excessive motion (>4mm) during the fMRI task (OBP *N*=3; OCP *N*=1); and/or missing sleep data (OBP *N*=1; OCP *N*=2). A comparison between the 46 included participants and the 17 participants excluded due to fMRI or sleep data loss can be found in Supplemental Table 1.

Assessment Procedures

Comprehensive clinical evaluations were conducted prior to a scanning visit. Participants and their parents were interviewed. Parental Axis I psychopathology was assessed using the Structural Clinical Interview for DSM-IV (SCID-I; First et al., 1997) and the Family History Screen (Weissman et al., 2000). Participant (offspring) Axis I psychopathology was assessed using The Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997). Interviewers were blind to participant status.

Before the scan, participants completed clinical and demographic questionnaires. All participants documented psychotropic medication use, and completed drug/alcohol/pregnancy screens, the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), the Snellen visual acuity test, the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and a modified version of the self-report Pittsburgh Sleep Quality Index (Buysse et al., 1989) to assess sleep patterns and quality in the prior week. Self-reported sleep was preferred for youth, as youth are more reliable reporters of their sleep than their parents (Short et al., 2013). Item responses pertaining to sleep

patterns on the modified one-week PSQI version (m-PSQI) are consistent with gold-standard daily sleep diary ratings (Broderick et al., 2013). Average sleep duration in the week prior to scan was derived from the m-PSQI. Pubertal status was assessed using a self-report questionnaire (Petersen et al., 1988). Parents completed the Mood and Feelings Questionnaire to assess depressive symptoms in the past two weeks in their children (MFQ-P; Angold *et al*., 1995), the Self-report for Childhood Anxiety Related Emotional Disorders to assess their anxiety symptoms in the past two weeks in their children (SCARED-P; Birmaher *et al.* 1997), and the Hollingshead scale to assess socioeconomic status (SES; Hollingshead, 1975). To evaluate aspects of mood dysregulation in their children, parents also completed the Parent General Behavior Inventory-10 Item Mania Scale to assess positive mood and energy dysregulation the past six months (PGBI-10M; Youngstrom et al., 2008) and the Child Affective Lability Scale - Parent Report to assess severity of mood lability (CALS-P; Gerson et al., 1996). Elevated scores on these mood dysregulation measures (PGBI-10M, CALS-P) have been linked to a BD diagnosis in youth (Birmaher et al., 2013; Findling et al., 2010) .

Neuroimaging

Reward Paradigm

A validated block-design functional magnetic resonance imaging paradigm (Bebko et al., 2014; Forbes et al., 2009; Manelis et al., 2016, In Press) was used to probe reward-related neural circuitry. Participants played a card number-guessing game that contained win, loss, and control guessing trials. The task was approximately 6 minutes. Participants had 3000 msec to guess via button press whether the value of a visually presented card was higher or lower than 5, with possible card values ranging from 1 to 9. For win and loss trials, after a choice was made the actual numerical value of the card (500 msec) and then outcome feedback (500msec; Win: green

upward-facing arrow; Loss: red downward-facing arrow) were visually presented. For control trials, participants pressed a button to the letter "X" (3000 msec), then viewed an asterisk (500 msec), followed by a yellow circle (500 msec). After each trial ended, participants viewed a fixation cross (3000 msec inter-trial interval). The paradigm contained 9 blocks: 3 win (each comprising 80% win, 20% loss trials), 3 loss (each comprising 80% loss, 20% win trials), and 3 control (no change in earnings) blocks. Guessing blocks (Win and Loss) had 5 trials with predetermined outcome order (*Win block*: win, win, win, loss, win; *Loss block*: loss, loss, win, loss, loss). Control blocks had 6 control trials. Participants were told that their performance on the card game would determine a monetary reward to be received at the end of the game; however outcome was fixed at $10 for all participants. Prior studies with this task have shown that participants were unaware of the fixed outcomes and believed their performance was due to chance (Forbes et al., 2009). Participants practiced the task and minimizing head movement in an fMRI simulator before scanning. Throughout practice and scanning, participants were verbally encouraged to perform to the best of their abilities and to minimize movement.

fMRI Data Acquisition and Preprocessing

Neuroimaging data were acquired using a Siemens MAGNETOM TrioTim 3T MR system. A high-resolution structural image (1x1x1mm) was acquired using MPRAGE (TR=2300 msec, TE=3.93 msec, FOV-256, FA=9 degrees, 192 slices). Blood oxygen-level dependent (BOLD) functional data were collected using a gradient-echo, echo-planar sequence (voxel size: 3.2x3.2x3.1mm, TR=2000 msec, TE=28 msec, FOV=205, FA=90°, 38 slices). These data comprised 178 volumes (TRs). A PC with E-prime software (Psychology Software Tools (PST), Pittsburgh, PA) controlled stimulus display.

Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm) was used to preprocess and analyze fMRI data. Preprocessing involved realignment, coregistration, segmentation, normalization into a standard stereotactic space (Montreal Neurologic Institute, MNI; http://www.bic.mni.mcgill.ca), and spatially smoothing using a Gaussian kernel (FWHM: 8mm).

fMRI Data Analyses: Activity

Neuroimaging data were analyzed using SPM8. At the first level analysis, individual whole brain statistical maps were computed to evaluate the contrasts of interest (win-control and loss-control). Our main focus was on examining relationships among group, sleep duration and neural activity to reward, thus the stimulus contrast of interest was the win-control contrast. We report findings for the loss-control contrast in supplemental materials (Supplemental Table 3). Movement parameters obtained from the realignment stage of preprocessing served as covariates of no interest.

Second level random-effects analyses were conducted in a ROI mask comprising key regions in reward circuitry: the bilateral ACC (BA24/32), mPFC (BA10), OFC (BA11), VLPFC (BA47), insula, and ventral striatum (VS; bilateral spheres centered on −9, 9, −8 and 9, 9, −8; radius=8mm; see Postuma and Dagher, 2006, Di Martino et al., 2008 for meta-analyses). The mask was created using the WFU PickAtlas (Maldjian et al., 2003). These neural regions are consistently implicated in reward processing in healthy and psychiatric samples (Caseras et al., 2013; Liu et al., 2011; Nusslock et al., 2012). Voxelwise regression analyses in SPM8 tested the effects of group status, sleep duration, and group*sleep duration interaction on BOLD response to win-control within the bilateral ROI mask. Group status was dummy-coded (OBP=0.5, OCP=-0.5). Sleep duration was mean-centered across both groups. A voxelwise threshold of $p<0.01$,

with a 3dClustSim cluster-level correction threshold of $p<0.05$ ($k=40$) to correct for family-wise error, was used for ROI analyses.

We extracted parameter estimates from the clusters displaying a significant effect of group, sleep duration and group*sleep interaction on brain activation using the eigenvariate tool in SPM8. These parameter estimates were imported into SPSS to compute R^2 and for post hoc simple slope analyses of significant group*sleep duration interaction effects. Simple slopes were computed using the SPSS PROCESS macro (Hayes, 2013).

fMRI Data Analysis: Psychophysiological Interactions (PPI)

A psychophysiological interaction (PPI) analysis was conducted in SPM8 to examine connectivity between a ventral striatum (VS) seed region and bilateral prefrontal-cingulo-insular ROI target regions that included bilateral ACC (BA24/32), mPFC (BA10), OFC (BA11), VLPFC (BA47), and insula. PPI provides information about the modulatory effects of the seed region in the context of an experimental condition on selected targets (Friston et al., 1997). We first created a PPI vector by multiplying mean time series from the bilateral VS seed region by the task condition vectors (win-control and loss-control). Single-subject first-level analyses were run using the PPI vector, bilateral VS time-course vector, and condition vector (win-control) as regressors. The resultant interaction terms were positively weighted in subsequent second level regression analyses given that our main hypotheses focused on coupling between the VS and target regions. As for the activity analyses above, the stimulus contrast of interest was win-control.

Group-level analyses for connectivity between the VS seed region and ROI target mask paralleled the BOLD activation analyses described above. A voxelwise threshold of $p<0.01$, with

a 3dClustSim cluster-level correction threshold of $p<0.05$ ($k=52$) to correct for family-wise error, was used for ROI analyses.

Correlations with Mood Dysregulation

Correlation analyses were conducted within each group to examine the extent to which extracted measures of BOLD activation and functional connectivity were associated with mood dysregulation measures. Analyses focused on regions displaying a significant group, sleep duration, or group*sleep duration interaction effects. Positive mood/energy dysregulation (PGBI-10M) and mood lability (CALS-P) were assessed. Statistical significance was set at $p=0.025$ (Bonferroni-corrected $p<0.05/2$). Symptom measure total scores were log transformed to better approximate a normal distribution. Due to the high frequency of zero scores on the PGBI-10M in OCP participants, correlation analyses were performed in OBP only for that measure. Exploratory correlations with depression (MFQ-P) and anxiety (SCARED-P) are included in the Supplemental Analyses.

Exploratory Analyses

Psychiatric medication use (e.g., Phillips et al., 2008) and current psychopathology (e.g., Whitton et al., 2014) have been shown to affect neuroimaging findings. Thus, we followed a prior method (Manelis et al., 2016; Manelis et al., 2015) to test the effects of medication use and current diagnosis on the BOLD activity and functional connectivity identified in the primary analysis. Using the extracted data previously described, we conducted regressions paralleling the main analyses on 1) participants without psychopathology and 2) unmedicated participants.

Lastly, we conducted exploratory whole-brain activity and VS connectivity to win-control to examine the extent to which patterns of whole-brain activity to this stimulus contrast were similar to activity and connectivity pattern in our a priori ROI masks (voxelwise threshold

of p < 0.005, cluster-level threshold of k=20) (Lieberman and Cunningham, 2009). As in the main analyses, we conducted voxelwise regressions in SPM to examine the effects of group (OBP vs. OCP), sleep duration, and group*sleep duration interaction on BOLD activity and VS connectivity to win-control.

Results

Demographic and Clinical Data

The two groups did not significantly differ with regard to sociodemographic features, including age, sex, SES, IQ, pubertal status and handedness (Table 1). Groups also did not differ on the majority of clinical characteristics, including Axis I disorders, depressive symptoms (MFQ-P), anxiety symptoms (SCARED-P), and sleep parameters (m-PSQI) (Table 1). However, relative to OCP, OBP exhibited greater symptoms of positive mood/energy dysregulation (PGBI-10M) and mood lability (CALS-P) (all *p*-values<.05). Across all participants, sleep duration was negatively correlated with age (r=-0.45, p=0.002) and pubertal status (r=-0.36, p=0.013), but not other demographic characteristics. Including age or pubertal status as covariates in fMRI analyses did not alter the pattern of neuroimaging findings. In OBP, sleep duration was negatively correlated with PGBI-10M (r=-0.43, p=0.031) and CALS-P (r=-0.40, p=.049). In OCP, sleep duration was not correlated with CALS-P and there was not a sufficient range of PGBI-10M scores within this group to perform a correlation. Rates of parental non-BD psychopathology did not differ between groups (Table 2).

fMRI: BOLD Activity

There was a significant effect of group on activation in the right posterior insula (peak voxel MNI xyz= [45, -1, -5], t_{42}=3.52, p=.001, corrected), with greater deactivation to win-control trials in OBP relative to OCP (Table 3, Fig. 1A, 1B). There was no significant effect of

sleep duration on BOLD activity. In support of our Aim 1a hypothesis that shortened sleep duration would be more strongly associated with reduced dorsal prefrontal activity in OBP relative to OCP, a significant group*sleep duration interaction effect was observed in left dorsal anterior mid-cingulate cortex (daMCC; peak voxel MNI xyz= [-3, 17, 37], t_{42}=3.57, p<.001, corrected) (Table 3, Fig. 1C, 1D). Post hoc analysis of the simple slopes revealed a positive association between sleep duration and daMCC activity in OBP (b=0.08[0.04], p=.029), and a negative association in OCP (b=-0.11[0.04], p=.013). Contrary to our Aim 1b hypothesis, we did not observe any group*sleep duration interactions for BOLD activity within ventral prefrontal cortical-striatal regions or insula.

fMRI: PPI

There was a significant effect of group on VS-left posterior insula functional connectivity (peak voxel MNI xyz= [-42, -4, -5], t_{42}=3.77, p<.001, corrected), with greater connectivity in OBP relative to OCP for win-control trials (Table 3, Fig. 2A, 2B). There was no significant effect of sleep duration on VS functional connectivity. However, in support of our Aim 1c hypothesis that shortened sleep duration would be more strongly associated with altered VS connectivity with ventral frontal cortical regions in OBP relative to OCP, there was a significant sleep duration*group interaction for VS-left anterior insula/VLPFC connectivity (peak voxel MNI xyz= [-36, 8, -11], t_{42}=3.11, p<.001, corrected) (Table 3, Fig. 2C, 2D). Post hoc analysis of simple slopes revealed a negative association between sleep duration and VS-left anterior insula/VLPFC connectivity in OBP (b= -0.09[0.04], p=.028), and a positive association in OCP (b= 0.12[0.04], p=.009).

Correlations between fMRI Measures and Mood Dysregulation

Our Aim 2 hypothesis that reward-related activation and connectivity patterns associated

with group status, sleep duration, or their interaction would correlate with elevated mood dysregulation symptoms in OBP was partially supported. BOLD activation within the right posterior insula and left daMCC was not related to mood dysregulation symptom measures. VS-left posterior insula connectivity was positively correlated with CALS-P (r=0.50, p=0.011) and PGBI-10M (r=0.52, p=0.007) in OBP, but not significantly related to mood dysregulation measures in OCP. VS-left anterior insula/VLPFC functional connectivity was positively correlated with CALS-P (r=0.47, p=0.016) and PGBI-10M (r=0.57, p=0.003) in OBP, but showed no relationship with mood dysregulation measures in OCP.

Exploratory Subgroup Analyses

Regression analyses in the subgroups of unmedicated participants (OBP *N*=23, OCP *N*=18) and participants without psychopathology (OBP *N*=16, OCP *N*=11) largely paralleled the pattern observed in main analyses. For BOLD activity analyses, OBP without psychopathology showed the same decreased pattern of right posterior insula activity as the larger group (OBP<OCP, b=-0.27[0.11], p=.027), although unmedicated OBP did not show this pattern of right posterior insula difference (b=-0.37[0.42], p=.375). There was a group*sleep duration interaction effect in the left daMCC (unmedicated participants: b=0.21[0.06], p=.001; participants without psychopathology: b=0.28[0.07], p=.001). Post hoc simple slope analyses were consistent with the main analyses for OBP (unmedicated OBP: b=0.10[0.04], p=.024; OBP without psychopathology: b=0.11[0.05], p=.009) and OCP (unmedicated OCP: b=-0.11[0.04], p=.016; OCP without psychopathology: b=-0.17[0.06], p=.020).

For the PPI analyses, there was a group effect for VS-left posterior insula functional connectivity (OBP>OCP; unmedicated participants: b=1.24[0.46], p=.011; participants without psychopathology: b=0.30[0.10], p=.027). There was a group*sleep duration interaction effect for

VS-left anterior insula/VLPFC functional connectivity (unmedicated participants: b=-0.21[0.06], p<.001; participants without psychopathology (b=-0.21[0.08], p=.018). Post hoc simple slope analyses were also generally consistent for OBP (unmedicated OBP: b=-0.09[0.04], p=.004; although not significant for OBP without psychopathology: b=-0.01[0.05], p=.814) and OCP (unmedicated OCP: b=0.13[0.04], p=.040; OCP without psychopathology: b=0.20[0.07], p=.006).

Exploratory Whole-Brain Analyses

Exploratory whole-brain regressions revealed patterns of activity and VS connectivity similar to those reported in the ROI analyses, as well as additional findings (See Supplemental Table 2).

Discussion

To improve our understanding of neurobehavioral mechanisms involved in the development of BD, the goal of this preliminary study was to examine associations between sleep duration, reward circuitry function, and symptoms of mood dysregulation in youth at high- and low-familial risk for BD (as a function of parental history of BD). In OBP without established BD, we sought to assess whether reduced sleep duration may represent a factor exacerbating functional abnormalities within reward-related neural circuitry, namely activity and connectivity among ventral prefrontal cortical-striatal and dorsal frontal regions. We used self-reported sleep duration, neuroimaging measures of reward processing circuitry, and parent-reported measures of mood dysregulation in non-BD OBP and OCP. Associations between sleep duration and reward-related neural activity and connectivity, and the moderating effect of parental history of BD, were examined. We also tested whether group-and sleep-related neural activity and connectivity patterns were associated with mood dysregulation.

In support of our Aim 1a hypothesis that shortened sleep duration would be more strongly associated with reduced dorsal prefrontal activity in OBP relative to OCP, we observed a relationship between sleep duration and daMCC activity that differed between groups. Shorter sleep duration was related to *greater* daMCC activity in OCP and *decreased* daMCC activity in OBP. The daMCC is proposed to play a key role in attentional/cognitive control (Bush et al., 2000). In healthy individuals, frontal neural regions supporting attentional control are highly susceptible to the effects of sleep loss (Ma et al., 2015; Muzur et al., 2002), but can display compensatory increases in activity depending on task characteristics (Chee and Choo, 2004; Drummond et al., 2005). Thus, the present pattern of findings may reflect a lack of compensatory response in OBP in the context of shorter sleep duration, while this compensatory response may have remained intact in OCP. Contrary to our Aim 1b hypothesis, and findings from total sleep deprivation studies (Gujar et al., 2011; Mullin et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011b), associations between sleep duration and activity within ventral prefrontal-striatal regions (vmPFC, OFC, insula, VS) to win-control were not detected here. This could be attributable to our focus on naturalistic sleep duration, rather than experimental sleep deprivation: increased activation has predominantly been observed in these regions under conditions of total sleep deprivation. We also observed that the right posterior insula (Chang et al., 2013) was more deactivated in OBP than OCP. Posterior insula activation was not associated with affective symptoms in either group. This region has been implicated in interoception and physiological reactivity during reward processing (Chang et al., 2013; Menon and Uddin, 2010). However, the group effect in the right posterior insula may have been influenced by current psychotropic medication use, as unmedicated participants did not display a significant group effect in this region. The differences in functioning of the daMCC and right posterior insula,

while not related to mood dysregulation, may reflect alternative risk processes, associated with disrupted cognitive control and interoceptive processing, linked to parental history of BD.

In support of our Aim 1c hypothesis that shortened sleep duration would be more strongly associated with altered VS connectivity with ventral frontal cortical regions in OBP relative to OCP, PPI analyses showed group and group*sleep duration interaction effects in key reward-related functional connectivity. OBP displayed increased VS-left posterior insula connectivity relative to OCP for win-control. A group*sleep duration interaction was observed for VS-left anterior insula/VLPFC connectivity, with shorter sleep duration associated with *greater* connectivity in OBP, but *lower* connectivity in OCP. Interestingly, the left posterior insula and left anterior insula/VLPFC regions partially overlapped (Figure 3). Together, these findings could indicate that OBP exhibit increased VS-left insula connectivity overall, with the ventroanterior subregion (Chang et al., 2013) and adjacent left VLPFC affected by sleep duration. The VS supports reward evaluation and anticipation (Knutson et al., 2001; O'Doherty, 2004), the anterior and posterior insula interact to modulate physiological reactivity to salient stimuli (Menon and Uddin, 2010), and the VLPFC is proposed to encode arousal during reward processing (e.g., Dolcos et al., 2004). Both the insula and VLPFC likely have excitatory afferent connections with the VS in humans, as indicated by homologs in animal models (Chikama et al., 1997; Sesack and Grace, 2010). The observed VS connectivity patterns thus suggest that OBP may encode reward cues as more salient/arousing than OCP, and that shorter sleep duration may exacerbate this phenomenon in OBP. Greater VS connectivity with both the left posterior insula and left anterior insula/VLPFC were also associated with elevated symptoms of mood dysregulation (e.g., mood lability, positive mood/energy dysregulation). By contrast, VS connectivity patterns in OCP were not significantly correlated with these symptoms. These

findings point to divergent neural mechanisms underlying mood dysregulation in OBP and OCP, but suggest that elevated VS-left insula/VLPFC connectivity to reward is a potential neural mechanism underlying risk for mood dysregulation in OBP.

The left lateralization of the observed striatal connectivity patterns is intriguing, given a growing number of studies reporting increased left VLPFC activation during reward processing in adult BD (for review see Phillips & Swartz, 2014; Nusslock et al., 2014), and are consistent with theories proposing a role of the left prefrontal cortex in encoding approach-related emotions (Pizzagalli et al., 2005). However, the present findings stand in contrast to prior work in OBP observing altered right VLPFC connectivity with pregenual cingulate gyrus (Singh et al., 2014) and bilateral VS (Manelis et al., 2016) during reward processing. The right VLPFC has been interpreted as serving an emotion regulatory function during reward processing (Singh et al., 2014; Manelis et al., 2016). Herein, given that sleep duration was differentially related to VS connectivity with the left anterior insula/VLPFC region, this could reflect a role of sleep duration in the modulation of encoding salient, approach-related emotions during reward processing.

Several limitations should be considered. The relatively small sample size affects statistical power, and may have limited our ability to detect weaker interaction effects. There were also a large number of analyses. Findings should be replicated in a larger sample. There was also no comparison group of healthy offspring of healthy parents, as our focus was on examining the impact of sleep duration on reward circuitry function in at-risk youth. Sleep-reward associations observed herein may not generalize to healthy youth. A very small number of participants were taking medications, which can influence neuroimaging measures (Phillips et al., 2008). Though, we note that the pattern of findings remained largely intact in the sub-group of unmedicated participants. The study design was also cross-sectional in nature, thus causal

associations cannot be inferred. Sleep duration was measured via self-report. Some evidence suggests that psychiatric samples can provide less reliable self-report estimates of sleep in comparison with objective estimates (Gonzalez et al., 2013). Our measure of sleep duration from the m-PSQI has been shown to be consistent with gold-standard daily sleep diary ratings, however (Broderick et al., 2013). Mood assessments included in the present study were parent-reported, which can be affected by parental mood at the time of rating (e.g., Birmaher et al., 2013). Clinician-rated mood assessments were not conducted on scan day. Future studies would benefit from incorporating clinician-rated mood assessments with parent- and self-report.

Future research designed to establish causal relationships among sleep, reward circuitry function, and mood dysregulation in at-risk youth is recommended. While reciprocal relationships among these phenomena likely exist, understanding the neurobehavioral pathways linking sleep to the initial emergence of mood dysregulation could provide opportunities for preventative sleep-focused treatments, and identify neural markers to serve as clinical outcomes. Longitudinal research is necessary to establish the hypothesized temporal patterns, particularly whether neuroimaging markers mediate relationships between sleep and mood dysregulation. Experimental manipulations of sleep would also hold great utility for establishing causal links. For example, sleep extension paradigms could be used to ascertain whether brain function and mood dysregulation are improved in high-risk youth with insufficient sleep.

While the focus in the present study was on sleep duration, it is also possible that other sleep parameters are relevant to the onset and course of BD. For example, instability of sleep-wake patterns is also common in BD (e.g., Ng et al., 2014), and a target of existing psychosocial interventions such as Interpersonal and Social Rhythm Therapy. Thus, future studies would

benefit from a more comprehensive sleep assessment, examining a wider set of sleep parameters using both objective and subjective measures.

This study is the first to our knowledge to establish a relationship between sleep duration and reward circuitry function in youth at high risk for BD. Parental history of BD moderated the association between sleep duration and reward-related left daMCC activity and VS-left anterior insula/VLPFC connectivity, while VS-left posterior insula connectivity was elevated in OBP relative to OCP. Elevated VS connectivity with both the left posterior insula and left anterior insula/VLPFC were correlated with greater mood dysregulation in OBP. This pattern of findings suggests that elevated VS-left insula connectivity during reward processing may represent a neural mechanism underpinning mood dysregulation in OBP. These results also indicate that reduced sleep duration could be one factor associated with increased of VS-left insula connectivity, shedding light on a potential neurobehavioral risk pathway for mood dysregulation in OBP. These findings, along with future longitudinal and experimental work, could provide neurobehavioral targets to guide preventative treatments in OBP.

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Table 1. Demographic, clinical, and sleep characteristics in offspring of bipolar parents (OBP) and offspring of control parents (OCP).

	OBP (N=25)	OCP (N=21)		
Demographic & Clinical	*Mean (SD) or N (%)*	*Mean (SD) or N (%)*	*Statistic*	*p*
Age (years)	14.20 (2.25)	13.95 (2.24)	t_{44}= 0.38	0.703
Sex (% female)	11 (44.0%)	11 (52.4%)	X^2 = 0.32	0.571
IQ (WASI)	100.40 (15.63)	101.62 (11.84)	t_{44}=-0.29	0.771
Pubertal Status (% Late/Post)	15 (60.0%)	14 (66.7%)	X^2 = 0.22	0.641
SES (Hollingshead)	2.68 (1.37)	3.43 (1.57)	t_{44}=-1.73	0.092
EHI Handedness (right)	22 (88.0%)	19 (90.5%)	X^2 = 2.22	0.329
MFQ-P Score	7.08 (9.51)	4.10 (3.52)	t_{44}= -0.77	0.449
SCARED-P Score	10.00 (6.30)	12.35 (12.48)	t_{43}= 1.42	0.165
PGBI-10M Score	2.40 (3.15)	0.81 (1.40)	t_{44}= 2.27	0.029
CALS-P Score	9.76 (11.11)	3.90 (4.59)	t_{43}= 2.39	0.022
Any Axis 1 Disorder	9 (36.0%)	10 (47.6%)	X^2= 0.64	0.425
Depressive Disorders	4 (16.0%)	3 (14.3%)	--	1.000
Anxiety Disorders	3 (12.0%)	5 (23.8%)	--	0.439
ADHD	4 (16.0%)	3 (14.3%)	--	1.000
Disruptive Behavior Disorder	1 (4.0%)	2 (9.5%)	--	0.585
Eating Disorder	2 (8.0%)	0 (0.0%)	--	0.493
>1 Axis 1 Disorders	4 (16.0%)	5 (23.8%)	--	0.711
Psychotropic Medication	2 (8.0%)	3 (14.3%)	--	0.648
Stimulant	1 (4.0%)	2 (9.5%)	--	0.585
Antidepressant	0 (0.0%)	1 (4.8%)	--	0.457
Antipsychotic	1 (4.0%)	0 (0.0%)	--	1.000
Past-Week Sleep (m-PSQI)				
Sleep Duration (hours)	8.00 (1.97)	7.58 (1.86)	t_{44}= 0.73	0.469
Bedtime	23:00 (2:52)	23:07 (1:40)	t_{44}=-0.15	0.878
Risetime	7:56 (2:22)	7:35 (1:49)	t_{44}= 0.59	0.557
Sleep Onset Latency (minute)	19.24 (24.64)	23.19 (21.55)	t_{44}=-0.57	0.569
Sleep Efficiency (%)	92.05 (12.21)	90.86 (10.01)	t_{43}= -0.35	0.726
m-PSQI Sleep Quality Score	3.64 (2.92)	4.95 (4.21)	t_{43}=1.23	0.226

Note. SD = Standard Deviation; -- = Fisher's Exact Test; t(df);WASI = Wechsler Abbreviated Scale of Intelligence; SES = socioeconomic status; EHI = Edinburgh Handedness Inventory; MFQ-P = Mood and Feelings Questionnaire–Parent Version; SCARED-P = Self-report for Childhood Anxiety Related Emotional Disorders–Parent Version; PGBI-10M = Parent General Behavior Inventory 10-item Mania Scale; CALS-P = Child Affective Lability Scale–Parent Version; ADHD = Attention-Deficit Hyperactivity Disorder; m-PSQI = Past-Week Pittsburgh Sleep Quality Index.

Table 2. Lifetime psychopathology for parents of OBP and OCP.

	Parents with BD (N=25)	Parents with non-BD psychopathology (N=21)		
	N (%)	*N (%)*	*Statistic*	*p*
Bipolar Disorder			$X^2 = 46.0$	<.001
Bipolar Disorder, type 1	18 (72%)	0 (0.0%)		
Bipolar Disorder, type 2	7 (28%)	0 (0.0%)		
Depressive Disorders	0 (0.0%)	11 (5.4%)	--	<.001
Anxiety Disorders	21 (76.2%)	16 (84.0%)	--	0.711
ADHD	4 (16.0%)	2 (9.5%)	--	1.000
Disruptive Behavior Disorder	4 (16.0%)	1 (4.8%)	--	0.357
Substance Use Disorder	17 (68.0%)	9 (42.9%)	$X^2 = 2.94$	0.087
Eating Disorders	3 (12.0%)	1 (4.9%)	--	0.614
Any non-BD Axis I pathology	23 (92.0%)	21 (100%)	--	0.493

Note. OBP = offspring of bipolar parents; OCP = offspring of control parents; ADHD= attention deficit hyperactivity disorder; BD=bipolar disorder; -- = Fisher's Exact Test.

Table 3. ROI regression analyses of group status, sleep duration, and group*sleep duration interaction effects on BOLD activity and PPI functional connectivity to win>control.

Comparison	Region	Slope	BA	Side	k	MNI Coordinates x	y	z	Statistic t(42)	*p*
BOLD Activation										
Group Effect	Posterior insula	-	13	R	57	45	-1	-5	3.52	.001
Sleep Duration Effect	--	--	--	--	--	--	--	--	--	--
Group*Sleep Duration Effect	daMCC	+	24,32	L	41	-3	17	37	3.22	<.001
PPI functional connectivity with ventral striatum seed										
Group Effect	Posterior Insula	+	13	L	59	-42	-4	-5	3.77	<.001
Sleep Duration Effect	--	--	--	--	--	--	--	--	--	--
Group*Sleep Duration Effect	Anterior insula/ VLPFC	-	13,47	L	89	-36	8	-11	3.32	.001

Note. ROI=region of interest; BOLD=blood oxygen level dependent; PPI=psychophysiological interaction; BA= Brodmann Area; -- indicates data not applicable; L = left; R = right; daMCC = dorsal anterior mid-cingulate cortex; VLPFC = ventrolateral prefrontal cortex; Group status was dummy coded OBP=0.5 and OCP=-0.5; k=cluster size in voxels; t(df).

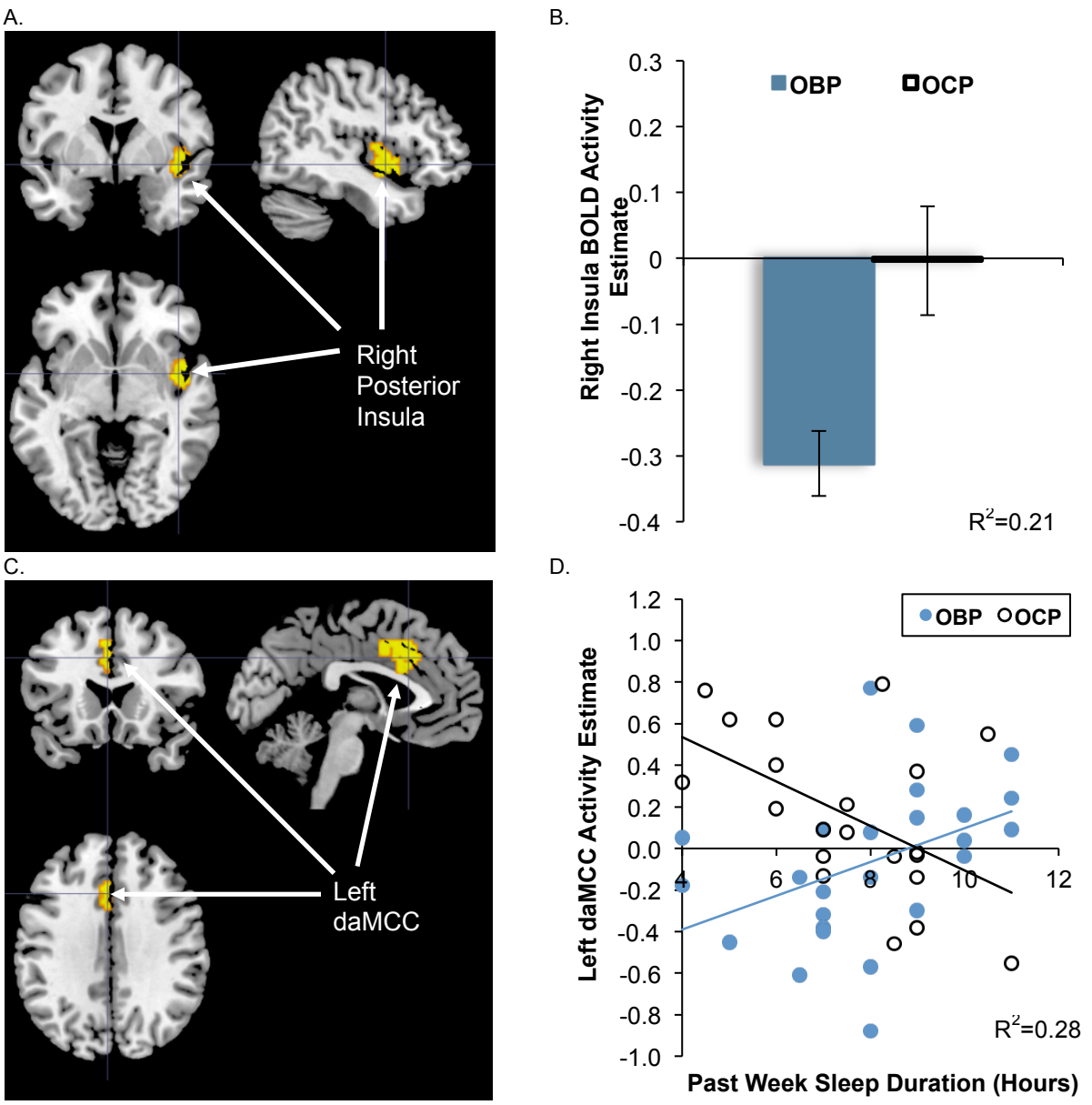

Figure 1. SPM regression analysis testing group, sleep duration, and group*sleep duration interaction as predictors of BOLD activity to win-control within the bilateral prefrontal-striatal ROI mask. **(A)** Significant group effect on BOLD activity in the right posterior insula [k=57, peak voxel MNI xyz= [45, -1, -5], t_{42}=3.52, p=.001]. **(B)** Extracted right insula peak BOLD activity estimates plotted by group; means and standard error bars are presented, R^2 represents variance explained for the overall regression. **(C)** Significant group*sleep duration interaction on left daMCC BOLD activity [k=41, peak voxel MNI xyz= [-3, 17, 37], t_{42}=3.57, p<.001]. **(D)** Extracted left daMCC BOLD activity estimates plotted versus sleep duration for group*sleep duration interaction, trend lines indicate simple slopes for each group, R^2 represents variance explained for the overall regression. OBP = offspring of bipolar parents; OCP = offspring of control parents; daMCC=dorsal anterior mid-cingulate cortex.

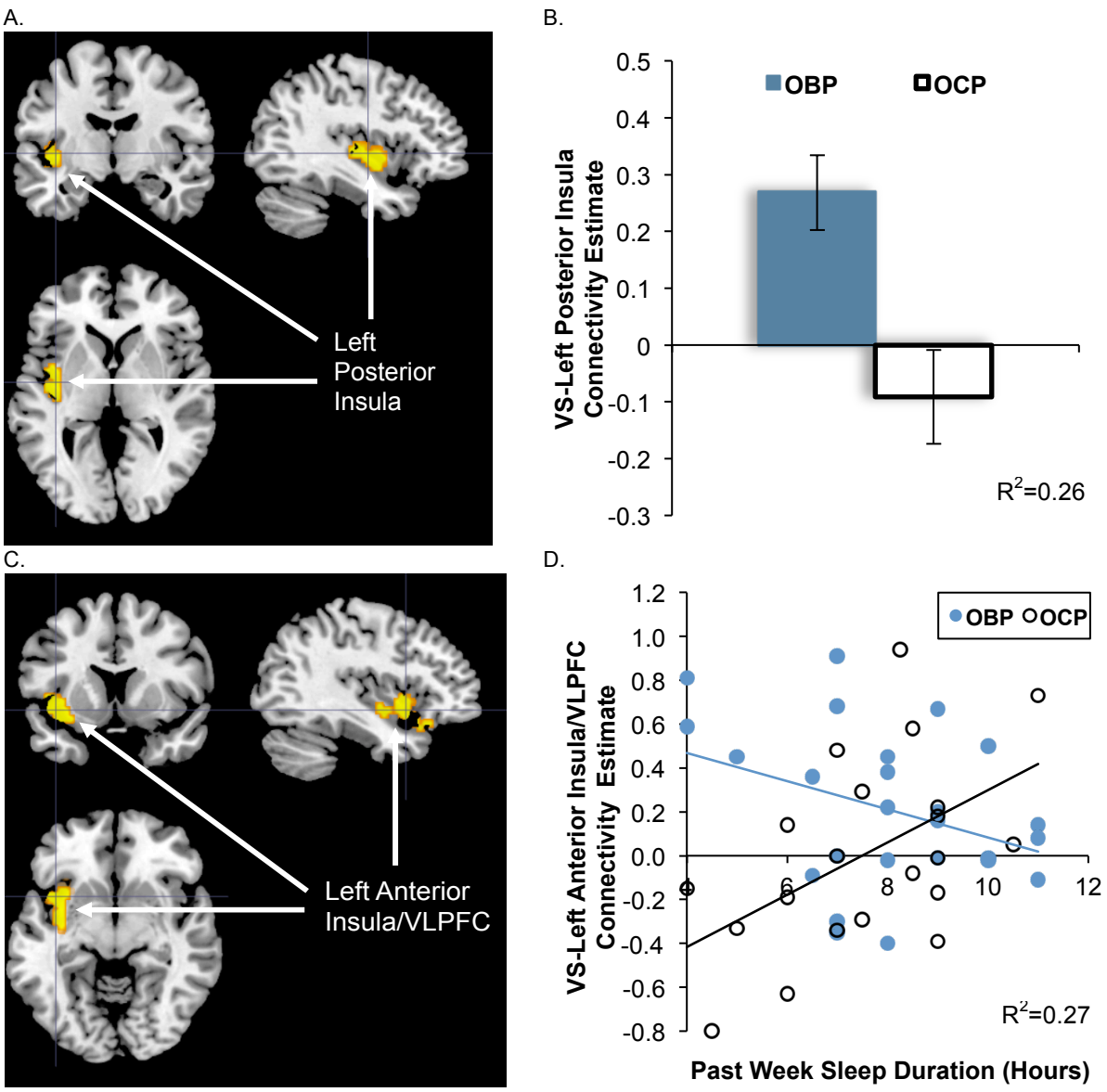

Figure 2. SPM regression analysis testing group, sleep duration, and group* sleep duration interaction as predictors of VS connectivity to win-control within the bilateral prefrontal-cingulo-insular ROI mask. **(A)** Significant effect of group status on VS connectivity with the left posterior insula: k=59, peak voxel MNI xyz= [-42, -4, -5], t_{42}=3.77, p<.001. **(B)** Extracted VS-Left posterior insula connectivity estimates displaying a significant difference between groups; means and standard error bars are presented, R^2 represents variance explained for the overall regression. **(C)** Significant group*sleep duration interaction for VS connectivity with the left anterior insula/VLPFC: k=89, peak voxel MNI xyz= [-36, 8, -11], t_{42}=3.11, p=.001. **(D)** Extracted VS-Left anterior insula/VLPFC connectivity estimates plotted versus sleep duration for group*sleep duration interaction, trend lines indicate simple slopes for each group, R^2 represents variance explained for the overall regression. OBP=offspring of bipolar parents; OCP=offspring of control parents; VS=ventral striatum; VLPFC=ventrolateral prefrontal cortex.

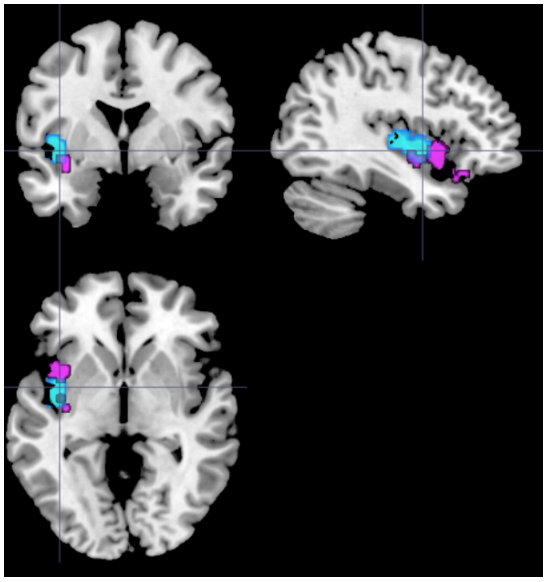

Figure 3. Overlap in group (blue – left posterior insula) and group*sleep duration interaction (violet – left anterior insula/ventrolateral prefrontal cortex) effects in PPI analysis of VS connectivity to win-control within the bilateral prefrontal-cingulo-insular ROI target mask. PPI = psychophysiological interaction; VS = ventral striatum; ROI = region of interest.

Supplementary Material

Supplemental Analyses

Excluded versus included participants

Sociodemographic, clinical, and sleep characteristics were compared between participants included in the present study (N=46) and participants excluded on the basis of missing/unusable neuroimaging or sleep data (N=17). Relative to included participants, excluded participants were younger, more often pre- to mid-pubertal, less anxious (SCARED), and had longer sleep onset latency. Other variables did not significantly differ between groups.

Activation and functional connectivity to loss>control

BOLD activity and PPI analyses to the loss>control contrast were examined using the same methods detailed in the main analyses for the win<control contrast. No significant effects of group, sleep duration, or group*sleep duration interaction were observed for BOLD activity and VS functional connectivity within the ROI masks (Supplemental Table 2). Whole-brain analyses of the loss>control contrast are reported in Supplemental Table 2.

Exploratory correlation analyses

Correlation analyses were conducted within each group to examine the extent to which extracted measures of BOLD activation and functional connectivity were associated with current anxiety (MFQ-P) and depression symptoms (SCARED-P). Analyses focused on regions displaying a significant group, sleep duration, or group*sleep duration interaction effects. Statistical significance for exploratory correlations was set at $p<0.05$. Symptom measure total scores were log transformed to better approximate a normal distribution.

Correlations with sleep duration. In OBP, sleep duration was negatively correlated with MFQ-P (r=-0.51, p=0.011), but not correlated with SCARED-P. In OCP, sleep duration negatively correlated with SCARED-P (r=-0.47, p=.035), but was not correlated with MFQ-P.

Correlations with fMRI measures. Left daMCC activity was positively correlated with SCARED-P in OCP (r=.515, p=.020), but was not related to anxiety or depressive symptoms in OBP. Right posterior insula activity was not related to anxiety/depressive symptoms in either group. The VS-left posterior insula functional connectivity pattern was positively correlated with SCARED-P (r=0.45, p=0.025) in OBP, but not significantly related to anxiety/depressive symptoms in OCP. VS-left anterior insula/VLPFC functional connectivity was positively correlated with MFQ-P (r=0.50, p=0.013) in OBP, but showed no relationship with anxiety or depressive symptoms in OCP.

Supplemental Table 1. Demographic, clinical, and sleep characteristics in offspring of bipolar parents (OBP) and control parents (OCP) who were included versus excluded in the study.

	Included OBP & OCP (N=46)	Excluded OBP & OCP (N=17)		
Demographic & Clinical	*Mean (SD) or N (%)*	*Mean (SD) or N (%)*	*Statistic*	*p*
Group Status (% OBP)	25 (54.3%)	9 (52.9%)	$X^2 = 0.01$	0.921
Age (years)	14.09 (3.34)	12.33 (2.41)	$t_{61} = 2.72$	0.009
Sex (% female)	22 (47.8%)	8 (47.1%)	$X^2 < 0.01$	0.957
IQ (WASI)	100.96 (13.89)	98.35 (10.96)	$t_{61} = 0.70$	0.489
Pubertal Status (% Late/Post)	31 (67.4%)	6 (35.5%)	$X^2 = 5.28$	0.022
SES (Hollingshead)	3.02 (1.50)	2.94 (1.48)	$t_{61} = 0.19$	0.850
EHI Handedness (right)	1.15 (0.46)	1.12 (0.33)	$t_{61} = 0.28$	0.782
MFQ-P Score	5.73 (7.49)	4.19 (9.48)	$t_{58} = 0.65$	0.515
SCARED-P Score	11.04 (9.5)	5.94 (6.07)	$t_{60} = 2.06$	0.044
PGBI-10M Score	1.67 (2.61)	2.57 (6.42)	$t_{58} = -0.77$	0.444
CALS-P Score	6.52 (8.83)	8.06 (13.59)	$t_{59} = -0.54$	0.593
Any Axis 1 Disorder	19 (41.3%)	7 (41.2%)	$X^2 < 0.01$	0.993
Depressive Disorders	7 (15.2%)	0 (0.0%)	--	0.175
Anxiety Disorders	8 (17.4%)	3 (17.6%)	--	1.000
ADHD	7 (15.2%)	5(29.4%)	$X^2 = 1.62$	0.203
Disruptive Behavior Disorder	3 (6.5%)	1 (5.9%)	--	1.000
Eating Disorder	2 (4.4%)	0 (0.0%)	--	1.000
>1 Axis 1 Disorders	9 (19.6%)	2 (11.8%)	--	0.712
Psychotropic Medication	5 (10.9%)	1 (5.9%)	--	1.000
Stimulant	3 (6.5%)	1 (5.9%)	--	1.000
Antidepressant	1 (2.2%)	0 (0.0%)	--	1.000
Antipsychotic	1 (2.2%)	0 (0.0%)	--	1.000
Past-Week Sleep (m-PSQI)				
Sleep Duration (hours)	7.81 (1.91)	8.92 (1.60)	$t_{56} = -1.84$	0.072
Bedtime	23:19 (1:42)	22:27 (1:17)	$t_{55} = 1.62$	0.110
Risetime	7:46 (2:08)	7:23 (1:19)	$t_{55} = 0.56$	0.581
Sleep Onset Latency (minute)	21.04 (23.11)	46.23 (59.44)	$t_{57} = -2.35$	0.022
Sleep Efficiency (%)	91.53 (11.12)	95.99 (6.01)	$t_{54} = -1.28$	0.208
m-PSQI Sleep Quality Score	4.22 (3.57)	3.09 (2.84)	$t_{54} = 0.98$	0.334

Note. SD = Standard Deviation; -- = Fisher's Exact Test; WASI = Wechsler Abbreviated Scale of Intelligence; SES = socioeconomic status; EHI = Edinburgh Handedness Inventory; MFQ-P = Mood and Feelings Questionnaire–Parent Version; SCARED-P = Self-report for Childhood Anxiety Related Emotional Disorders–Parent Version; PGBI-10M = Parent General Behavior Inventory 10-item Mania Scale; CALS-P = Child Affective Lability Scale–Parent Version; ADHD = Attention-Deficit Hyperactivity Disorder; m-PSQI = Past-Week Pittsburgh Sleep Quality Index.

Supplemental Table 2. Whole-brain regression analyses for BOLD activity and PPI functional connectivity to win-control

Comparison	Region	Slope	BA	Side	k	MNI Coordinates			t(42)	*p*
						x	y	z		
BOLD Activation										
Group Effect	Precuneus	+	7	R	59	9	-49	70	3.82	<.001
	Primary Visual	+	17, 19	R	181	39	-79	10	3.54	<.001
	Pregenual cingulate	-	32	LR	74	0	32	-5	4.11	<.001
	Caudate	-	48	R	42	12	2	10	3.94	<.001
	Insula	-	13	R	47	45	-1	-5	3.27	.001
Sleep Duration Effect	Visual association cortex	+	18, 23	R	35	27	-58	4	4.42	<.001
	Parahippocampal gyrus	+	36	R	106	6	-40	-2	4.36	<.001
	Posterior cingulate	+	30	L	35	-18	-49	4	3.85	<.001
	Medial PFC	+	10	R	24	21	68	7	3.79	<.001
	Visual association cortex	+	18	R	64	30	-94	7	3.79	<.001
	Visual association cotex	+	18	L	161	-9	-100	-8	3.61	<.001
	Superior parietal lobule	+	7	L	23	-27	-67	55	3.32	<.001
	Superior temporal gyrus	-	38	L	95	-51	14	-20	4.63	<.001
	Doral and ventral posterior cingulate cortex	-	31, 23	R	74	15	-46	37	4.30	<.001
	Superior Frontal Gyrus	-	8	L	113	-30	11	25	4.22	<.001
	Hippocampus	-	54	R	20	24	-16	-8	3.88	<.001
	Dorsolateral PFC	-	9	R	107	30	35	28	3.75	<.001
	Insula	-	13	R	24	30	-19	10	3.58	<.001
	Superior Frontal Gyrus	-	8	R	34	33	8	31	3.44	.001
	Insula	-	13	L	20	-27	14	4	3.43	.001
	Primary sensory	-	1	R	51	45	-22	31	3.36	.001
	Primary sensory	-	1	R	21	51	-22	52	3.05	.002

	Inferior frontal gyrus; premotor cortex	+	44, 6		67	-60	11	25	4.39	<.001
	Mid-cingulate cortex, dorsolateral PFC	+	9, 8, 32	LR	240	27	38	31	3.99	<.001*
	Cerebellum	+	n/a	L	39	-33	-49	-23	3.70	<.001
	Sensory association area	+	5	L	24	-6	-37	55	3.51	.001
	Premotor cortex	+	6	L	24	-9	2	70	3.38	.001
	Inferior frontal gyrus	+	8, 44	R	37	36	5	25	3.35	.001
	Medial PFC	+	9	L	27	-3	44	46	3.24	.001
Group*Sleep Duration Effect	Lateral occipital gyrus	-	19	R	923	39	-64	1	6.19	<.001*
	Hippocampus, Visual association cortex	-	54, 18	L	458	-21	-40	1	4.82	<.001*
	Visual association aortex	-	18	L	31	-18	-88	-11	4.15	<.001
	Caudate	-	48	R	252	27	-34	7	4.10	<.001*
	Medial PFC	-	10	R	23	21	68	10	4.02	<.001
	Posterior cingulate cortex	-	n/a	L	22	-6	-28	22	3.67	<.001
	Orbitofrontal cortex	-	11	R	35	12	50	-14	3.60	<.001
	Medial PFC	-	10	L	24	-36	56	1	3.55	<.001
	Inferior parietal lobule	-	39	L	20	-51	-58	46	3.26	.001
PPI functional connectivity with ventral striatum seed										
	Primary sensory, Superior temporal gyrus	+	1, 22	L	862	-60	-16	25	4.44	<.001*
	Primary auditory	+	22	R	197	45	-31	4	3.64	<.001
Group Effect	Premotor cortex	+	6	R	40	-36	8	46	3.59	<.001
	Superior temporal gyrus	+	22, 38	L	115	51	-1	-5	3.46	.001
	Superior parietal lobule	+	7	L	20	-30	-49	55	2.98	.001
Sleep Duration Effect	--	--	--	--	--	--	--	--	--	--

Group*Sleep Duration Effect	Insula	-	13	L	220	-33	-1	-26	5.05	<.001
	Thalamus	-	50	L	137	-12	-16	25	3.47	<.001
	Superior parietal lobule	-	6	R	30	60	5	34	3.74	<.001
	Hippocampus	-	54	L	78	-36	-28	-8	3.35	<.001
	Primary Motor	-	40, 4	L	102	-51	-25	25	3.33	<.001
	Primary Motor	-	4	R	31	36	-10	25	3.31	<.001
	Dorsal anterior cingulate cortex	-	24	R	44	6	23	19	3.29	.001
	Mid-cingulate cortex	-	32	R	31	12	5	37	3.28	.001
	Mid-cingulate cortex	-	24	LR	34	0	-16	40	3.28	.001
	Amygdala	-	53	R	28	24	-1	26	3.19	.001
	Premotor cortex	-	6	L	31	-54	-1	28	3.31	.001
	Superior and middle temporal gyrus	-	21, 22	L	24	-54	-4	-14	3.23	.001

Note. BOLD = blood oxygen level dependent; PPI = psychophysiological interaction; BA= Brodmann Area; -- indicates data not applicable; L = left; R = right; PFC = prefrontal cortex; Group status was dummy coded OBP=0.5 and OCP=-0.5; *indicates cluster significant at a threshold of voxelwise p<.005, clusterwise FWE-corrected p<.05.

Supplemental Table 3. ROI and whole-brain regression analyses for BOLD activity and PPI functional connectivity to loss-control

Comparison	Region	Slope	BA	Side	k	MNI Coordinates x	y	z	t(42)	*p*
ROI Analysis										
BOLD Activation										
Group Effect	no significance									
Sleep Duration Effect	no significance									
Group*Sleep Duration Effect	no significance									
PPI functional connectivity with ventral striatum seed										
Group Effect	no significance									
Sleep Duration Effect	no significance									
Group*Sleep Duration Effect	no significance									
Whole-brain Analysis										
	Region	Slope	BA	Side	k	x	y	z	t(42)	*p*
BOLD Activation										
Group Effect	Superior Frontal Gyrus	+	8	R	45	30	29	49	4.75	<.001
	Dorsal PFC	+	9	R	20	15	50	40	3.43	.001
	Mid-cingulate cortex	-	24, 32	R, L	101	3	17	25	3.99	<.001
	Posterior cingulate cortex	-	31	L	25	-12	-40	43	3.47	.001
Sleep Duration Effect	Visual association cortex	+	18	R	102	21	-73	-8	3.91	<.001
	Visual association cortex	+	18	L	61	-15	-70	-8	3.63	<.001
	Fusiform area	+	37	R	29	54	-70	-2	3.62	<.001
	Primary visual	+	19	L	64	-27	-88	13	3.53	.001
	Visual association cortex	+	18	R	27	33	-85	7	3.02	.002
	Anterior cingulate cortex	-	24	L	179	-3	8	28	4.44	<.001
	Superior Frontal Gyrus	-	8	R	242	27	29	40	3.82	<.001*

	Lateral PFC	-	45	R	45	48	29	7	3.80	<.001
	Inferior parietal lobule	-	39	L	29	48	-55	49	3.75	<.001
	Posterior cingulate cortex	-	23	R	28	6	-43	31	3.18	.001
Group*Sleep Duration Effect	Thalamus	+	50	R	100	6	-1	1	4.74	<.001
	Premotor cortex	+	6	R	20	30	-22	70	4.29	<.001
	Fusiform	+	37	L	45	-39	-37	-17	4.00	<.001
	Insula, Superior temporal gyrus	+	13, 38	R	25	36	2	-20	3.82	<.001
	Cingulate cortex	+	24	L	90	-15	17	28	3.75	<.001
	Lateral PFC	+	44	R	56	30	11	19	3.75	<.001
	Cerebellum	+	--	L	42	-30	-46	-29	3.61	<.001
	Sensory association cortex	+	5	L	27	-6	-34	58	3.60	<.001
	Thalamus	+	50	L	36	-24	-28	10	3.55	<.001
	Insula	+	13	R	42	33	-13	10	3.53	.001
	Premotor cortex	+	6	L	25	-48	-4	19	3.19	.001
	Superior parietal lobule	-	7	L	47	-18	-79	49	3.74	<.001
	Lateral occipital gyrus	-	19	R	89	45	-73	16	3.50	.001
	Middle frontal cortex	-	10	R	28	27	65	10	3.38	.001

PPI functional connectivity with ventral striatum seed

Group Effect	Superior temporal gyrus	+	38	R	56	54	8	-23	3.28	.001
	Amygdala	+	53	L	31	-27	2	-23	3.00	.001
Sleep Duration Effect	Middle frontal cortex	+	10	L	34	-6	65	25	3.52	.001
Group*Sleep Duration Effect	Hippocampus/ Amygdala	-	53, 54	L	44	-33	-7	-23	3.69	<.001
	Hippocampus	-	-	L	27	-15	-16	-8	3.48	.001
	Dorsal PFC	-	9	L	23	-21	32	22	3.31	.001

Note. BOLD = blood oxygen level dependent; PPI = psychophysiological interaction; ROI Analysis voxelwise p<.01, 3dClustsim-corrected clusterwise p<.05; Whole Brain Analyses voxelwise p<.005, k=20; BA= Brodmann Area; L = left; R = right; PFC = prefrontal cortex; Group status was dummy coded OBP=0.5 and OCP=-0.5; *indicates cluster significant at a threshold of voxelwise p<.005, clusterwise FWE-corrected p<.05.

Highlights:

- Offspring of bipolar parents (OBP) exhibit altered reward circuitry function.
- Sleep duration predicts altered activity and striatal connectivity to wins in OBP.
- Sleep duration is related to mood dysregulation in OBP.
- Striatal connectivity is related to mood dysregulation in OBP.
- Altered striatal connectivity may link sleep loss to mood dysregulation in OBP.