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Research paper

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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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 (9–17 yr) 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.

1. 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

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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, 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.

2. Methods

2.1. 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