Published in final edited form as:

Clin Psychol Rev. 2012 November ; 32(7): 650–663. doi:10.1016/j.cpr.2012.07.003.

Overlapping prefrontal systems involved in cognitive and emotional processing in euthymic bipolar disorder and following sleep deprivation: A review of functional neuroimaging studies

Benjamin S McKenna^{a,b} and Lisa T Eyler^{a,b}

^aMental Illness Research, Education, and Clinical Center, Veterans Affairs San Diego Healthcare System, San Diego, California 92161

^bDepartment of Psychiatry, University of California, San Diego, California 92161

Abstract

Prefrontal cortex (PFC) mediated cognitive and emotional processing deficits in bipolar disorder lead to functional limitations even during periods of mood stability. Alterations of sleep and circadian functioning are well-documented in bipolar disorder, but there is little research directly examining the mechanistic role of sleep and/or circadian rhythms in the observed cognitive and emotional processing deficits. We systematically review the cognitive and emotional processing deficits reliant upon PFC functioning of euthymic patients with bipolar disorder and in healthy individuals deprived of sleep. The evidence from two parallel lines of investigation suggests that sleep and circadian rhythms may be involved in the cognitive and emotional processing deficits seen in bipolar disorder through overlapping neurobiological systems. We discuss current models of bipolar highlighting the PFC-limbic connections and discuss inclusion of sleep-related mechanisms. Sleep and circadian dysfunction is a core feature of bipolar disorder and models of neurobiological abnormalities should incorporate chronobiological measures. Further research into the role of sleep and circadian rhythms in cognition and emotional processing in bipolar disorder is warranted.

Keywords

Bipolar Disorder; Sleep; Cognition; Emotional Processing; Prefrontal Cortex

Introduction

Bipolar disorder (BD)¹ is a complex mental illness characterized by vacillations of mood between the highs of mania and the lows of depression with periods of relatively normal mood in between. Alterations of brain structure and function combined with environmental factors (e.g., stressors, sleep deprivation) are thought to cause a dysregulation of mood, sleep, cognition, endocrine function, and motor systems forming complex and dynamic interactions (Catapano, Chen, Jing, Zarate Jr., & Manji, 2009). Additionally, there is considerable heterogeneity of clinical characteristics including the frequency of mood cycling, age of first occurrence of symptoms, and the degree to which depressive and manic episodes co-occur (mixed states), which adds to the complexity of the disorder. The

Corresponding Author: Benjamin S McKenna, Ph.D., 3350 La Jolla Village Drive, San Diego, CA 92161 Mail Code: 151B, Phone: 858-552-8585 ext: 6992, bmckenna@ucsd.edu.

¹Abbreviations: bipolar disorder (BD); prefrontal cortex (PFC); functional magnetic resonance imaging (fMRI); circadian locomotor output cycles kaput (CLOCK); period homologue (PER); rapid eye movement (REM); non-REM (NREM); slow wave sleep (SWS).

multifaceted nature of symptoms experienced by those with BD leads to difficulties with everyday functioning in both social and occupational arenas, with cognitive and emotional processing deficits playing a particularly important role in these difficulties (Bearden et al., 2011; Bora, Yucel, & Pantelis, 2009; Torres, Boudreau, & Yatham, 2007). Cognitive impairments in several domains have been observed in BD (Glahn et al., 2010; Kurtz & Gerraty, 2009; Martinez-Arán et al., 2004) and many of these deficits have been linked to functional outcome (Bearden, Woogen, & Glahn, 2010). Furthermore, in addition to detrimental effects of high and low mood on social and vocational achievement (Simon, Bauer, Ludman, Operskalski, & Unutzer, 2007), deficits in emotional processing at a more basic level may not only result in mood instability, but may directly impact everyday functioning (Gopin, Burdick, DeRosse, Goldberg, & Malhotra, 2011; K. Nilsson, Jorgensen, Craig, Straarup, & Licht, 2010). While functional disability and cognitive/emotional processing deficits are most severe during a mood episode, many patients continue to have poor functioning and altered cognitive/emotional processing during periods of remission or euthymia (Gopin et al., 2011; Robinson & Ferrier, 2006). Sleep/circadian impairment is also prevalent in BD patients, even when clinical symptoms are in remission (Harvey, 2008). Several lines of research suggest that sleep/circadian disturbance is a core feature of BD related to many aspects of the disease progression and symptoms such as emotional dysregulation (for a review see Murray & Harvey, 2010). This is not unsurprising considering the close link between sleep timing, circadian disruption, and mental health (Wulff, Gatti, Wettstein, & Foster, 2010). Despite this long-recognized association, the causal role of sleep in brain function has been debated. Recently, there have been remarkable breakthroughs in our understanding of the neural and genetic basis for sleep and circadian rhythm functioning in the healthy brain and the relationship of these to normal cognitive and emotional operations. Unfortunately, there is little research directly examining the mechanistic role of sleep and/or circadian rhythms in the cognitive and emotional processing deficits seen in BD. Considering the emerging findings that sleep and circadian rhythms play an important role in cognitive and emotional functioning more generally, the dearth of research on this topic in BD is unfortunate, but provides an exciting opportunity for future studies.

Review Aims

This paper aims to systematically review the literature examining the cognitive and emotional processing in BD and sleep specifically involving the prefrontal cortex (PFC) neural circuitry in an attempt to postulate possible roles of sleep and circadian dysfunction in the PFC-mediated cognitive and emotional processing sequelae of BD. Several excellent review articles have already examined the broader literatures covering bipolar and cognitive/emotional processes, sleep and cognitive/emotional processes, and bipolar and sleep/circadian rhythms (Bearden, Hoffman, & Cannon, 2001; Chen, Suckling, Lennox, Ooi, & Bullmore, 2011; Murray & Harvey, 2010; Walker, 2009). Our more specific goal is to examine findings from these literatures implicating the PFC as a core neural structure in both BD and sleep. In light of a lack of research directly examining the mechanistic role of sleep and circadian rhythms in the cognitive/emotional processes of BD, we chose to focus this review on the following areas: 1) *Prefrontal Cortex*: Although both sleep disruption and BD are likely to influence multiple neural systems in the brain, the PFC plays an important role in higher order cognitive and emotional processing. Further, abnormalities within this region have been highlighted as core features of BD and, independently, sleep. Thus, the PFC is an area where interactions between cognitive and emotional processing, BD, and sleep disturbance are likely to occur. 2) *Euthymic Bipolar Patients*: We chose to focus only on studies of euthymic bipolar patients in order to examine trait-like PFC brain-behavior changes in the disorder that may be impacted by sleep/circadian disruption, independent of mood disruption. 3) *Sleep Deprivation*: The vast majority of studies examining the

relationship between sleep and PFC functioning employ sleep deprivation protocols in healthy adults. By depriving an individual of sleep and measuring the change in brain response, researchers are able to isolate brain regions that are thought to play a role in the interaction between sleep and cognition. Therefore, we chose to examine sleep deprivation studies in healthy adults in order to draw parallels between the impact of BD and sleep disruption in PFC-mediated functions. While studies of sleep disordered populations (e.g., insomnia and obstructive sleep apnea) also yield valuable information about the underlying neural correlates of cognitive and emotional processes, they are confounded by clinical characteristics of the studied population.

Article Inclusion Criteria

The relevant articles were searched using Pubmed and Psychinfo with the following search terms: 1) Bipolar and cognit* (or emot*), and prefrontal (or executive function); 2) sleep, cognit* (or emot*), and prefrontal (or executive function); 3) circadian, cognit* (or emot*), and prefrontal (or executive function); and 4) bipolar, sleep, cognit* (or emot*), prefrontal (or executive function). For each search the findings yielded: 1) 355 studies with respect to BD and cognition and 147 with respect to emotion; 2) 238 studies with respect to sleep and cognition and 67 with respect to emotion; 3) 39 studies with respect to circadian rhythms and cognition and 8 with respect to emotion; and 4) 7 studies with respect to sleep, BD, and cognition and 3 studies with respect to emotion. To narrow these findings for the aims of this review, inclusion criteria for all studies were that they be published in peer-reviewed journals in English, included adult participants (as opposed to pediatric or geriatric), and included cognitive or emotional data pertaining specifically to the PFC including tasks of executive functions. For articles pertaining to BD, studies were further required to include data from a BD patient group in a euthymic state and include a healthy comparison group. For studies pertaining to sleep deprivation, studies were further required to include data from young healthy individuals without neurological or mental health issues (including sleep disorders). Lastly, review and meta-analysis papers covering cognitive and/or emotional functioning in bipolar, sleep, or circadian rhythms were also included.

We first present a brief primer of the PFC and the sleep/circadian system to provide the necessary background information for this review. We then discuss the evidence linking sleep and circadian rhythms with BD highlighting the impact of sleep and circadian disruption in the disorder. Next, we review the overlapping deficits in cognitive and emotional processing dependent upon PFC functioning and overlapping genetics observed in euthymic BD patients and healthy individuals who are sleep deprived. Lastly, we discuss models of PFC-limbic connections in BD that provide a theoretical framework in which to include sleep and circadian disruption through PFC-mediated neural circuitry based on the parallels between findings in sleep and BD literatures. We encourage further research to critically examine sleep and circadian factors in BD patients to better understand not only how sleep influences the cognitive and emotional processes of BD, but also how improving sleep and stabilizing circadian rhythms can improve cognitive/emotional performance, and by extension, functional status.

Prefrontal Cortex and the Sleep/Circadian System Primer

It is outside the scope of this review to discuss the structural and functional complexity of the PFC or all the complex behavioral and neural processes that control human sleep and circadian rhythms. However, it is important to review the core concepts of organization of the PFC and how sleep and circadian rhythms are controlled through neurobiology and environmental factors to better understand the role that sleep/circadian functioning may have in the cognitive and emotional processing deficits seen in BD reliant upon the PFC.

Anatomical and Functional Heterogeneity of the Prefrontal Cortex

The PFC is sometimes treated as a homogenous brain structure, though this is not the case. There is a multitude of evidence that the PFC is neither structurally nor functionally homogenous (Cabeza & Nyberg, 2000; D'Esposito, Postle, Ballard, & Lease, 1999). The PFC comprises the majority of the frontal lobes lying anterior to the central sulcus excluding the primary and association motor cortices. Structurally, the PFC has been subdivided by cytoarchitecture and/or gross anatomic markers into subregions with varying specificity (Ongur, Ferry, & Price, 2003; Petrides & Pandya, 1994, 1999, 2002). For the purposes of this review, we refer to the 'classical' PFC regions reported in the literature including the dorsolateral PFC, ventrolateral PFC, anterior PFC, medial PFC, and within this region, the orbitofrontal cortex (see figure 1). There have been many studies implicating the medial PFC and orbitofrontal cortex in controlling emotional processes in a top-down manner, which are in turn modulated by attentional centers in dorsolateral PFC (Rolls & Grabenhorst, 2008). Further, PFC subregions play distinct roles in many cognitive processes that are commonly termed 'executive' functions. These include shifting, planning, prioritizing/updating information within working memory, and decision making abilities; which are, in turn, based upon other executive cognitive capacities such as top-down attentional processes, maintaining information within working memory, verbal fluency, and behavioral inhibition (Fuster, 1997; Goldberg, 2001). Additionally, by definition, higher-order executive functions rely upon other basic cognitive systems in the brain to adequately operate (e.g., sensory regions), and reciprocal connections with these regions must be considered when examining changes to these higher-order cognitive regions in studies.

Sleep and Circadian Rhythms

The sleep-wake cycle is controlled by two separate processes: 1) a process involving an endogenous circadian time-keeping system (known as process C) and 2) a wake-dependent homeostatic build-up of sleep pressure (known as process S). The approximately 24 hour rhythm of process C interacts with process S where sleep pressure builds the longer we are awake and dissipates while we sleep. Process S and process C operate in synchrony under normal conditions to control sleep and wake states during the appropriate time of day (e.g., being awake during the day and sleeping during the night), though this interaction is not fully understood (Czeisler, Buxton, & Khalsa, 2005). Process C is largely controlled by a central circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus and is comprised of a complex, interacting network of transcription factors that collectively maintain rhythmic expression of their target genes over ~24 hour cycles through multiple feedback loops. In turn, these genes regulate rhythmic behaviors like sleep/wake cycles, metabolic activity, and daily endocrine oscillations throughout the body. The circadian clock is composed of about 20 "core clock genes" that have been well-studied in animal models of circadian rhythms and sleep disorders. Additional peripheral feedback loops exist in many cells and organs of the body and regulate the core SCN feedback loop stabilizing a ~24 hour rhythm (Ko & Takahashi, 2006). An important structural concept of this network is that it forms an open system that can be externally influenced. The endogenous rhythm is not exactly 24 hours. A process called entrainment sets the circadian rhythm to a 24 hour period keeping in appropriate phase with astronomical day length and seasonal shifting. Entrainment occurs via environmental events termed *zeitgebers* that directly affect the phase of the internal circadian system. *Zeitgebers* include arousal level, social cues, meals, and sleep deprivation, just to name a few. However, the most prominent and influential *zeitgeber* is the daily alternation of light and dark (Roennebert & Foster, 1997). The SCN predominately receives light and dark information directly from the eyes through the retinohypothalamic tract. Light information from the eyes also indirectly acts upon the circadian system via arousal brain systems. Disruption of clock genes and/or ablation of the SCN in animals leads to various abnormalities in behaviors that are typically

rhythmic (e.g., period changes or arrhythmias), many of which are now well characterized. Additionally, several neurotransmitters are involved in maintaining wakefulness and in the different stages of sleep (España & Scammell, 2011). Sleep is characterized by different stages that can grossly be divided into rapid eye movement (REM) and non REM (NREM) sleep. Within NREM sleep, there are several substages including N1, N2, and N3 [or slow wave sleep (SWS)] that are defined by electrical activity of cortical and subcortical neural structures. Throughout a normal night of sleep, humans cycle through the different stages from NREM to REM (approximately 90 minutes per cycle) with predominantly more NREM sleep observed in the beginning of the night and more REM sleep observed at the end of the night (Shneerson, 2000; Silber et al., 2007). While sleep is vital for brain and body alike, centrally sleep and circadian function are brain-controlled phenomena. Thus, over the past few decades there has been a resurgence of sleep/circadian research within the neurosciences with a focus on cognition and emotion (Walker, 2009).

Sleep and Circadian Disruption in Bipolar Disorder

Abnormalities in sleep timing and architecture are recognized as common co-morbidities in numerous psychiatric disorders, including BD. It is important to stress that sleep disruption is tightly associated with an increase in susceptibility in psychiatric disorders, and is not merely the result of an individual's frustration at failing to initiate or sustain sleep (Wulff et al., 2010). Most of what we know about the basic biology of sleep and the circadian system is based on research conducted with individuals who do not have significant psychopathology, since experiments that severely disrupt or dysregulate sleep and rhythms are not suited for individuals with BD due to potential adverse side effects. Further complicating experimental studies of the role of sleep in BD is the considerable variation in clinical characteristics among individuals with the disorder. BD patients can vary greatly in the severity of their sleep/circadian disruptions at different periods of the disorder (i.e., mania, depression, or euthymia). With these experimental constraints in mind however, recent studies have begun to better understand sleep/circadian dysfunction in BD. A better understanding of the sleep and circadian system in BD is important considering that disruption of sleep/circadian control leads to wide-spread effects on neural and neuroendocrine functioning, which in turn affects cognitive and emotional processing among other systems in the body (Maquet, 1995). Indeed, two review papers have surveyed this literature and provided models of the close interaction between sleep/circadian functioning and the symptoms of BD (see Harvey, 2008; Murray & Harvey, 2010 for more detailed explanation). Also, the Diagnostic and Statistical Manual of Mental Disorder – Fourth Edition Text Revision lists a decreased need for sleep as a criterion for hypomanic and manic episodes and insomnia or hypersomnia for a criterion in bipolar depression (American Psychiatric Association, 2000). Findings suggest that sleep and circadian rhythm abnormalities are a core feature of BD present during periods of euthymia. Studies utilizing actigraphy to measure sleep-wake patterns find that euthymic BD patients have sleep disturbance characterized by more sleep fragmentation and disruption of circadian rhythms (S. Jones, Hare, & Evershed, 2005). Further, individuals at high risk for BD exhibit greater variability in duration of sleep and significantly later, and more variable, bedtimes relative to comparison participants (Ankers & Jones, 2009). In terms of the circadian system, patients generally report themselves as more evening-types suggesting a trait-like phase delay in the circadian system in BD (Wood et al., 2009). Supporting this theory is delayed melatonin secretion in euthymic BD patients (Nurnberger et al., 2000), which is associated with a delayed sleep phase. Altered sleep and circadian disruption often precedes a bipolar mood episode and worsens throughout the episode (Bauer et al., 2006; Jackson, Cavanagh, & Scott, 2003). As such, studies suggest a longitudinal association between disturbed sleep and subsequent development of BD, although the majority of these studies are retrospective (see Ritter, Marx, Bauer, Lepold, & Pfennig, 2011 for a review). Overall, studies examining

sleep in euthymic BD patients demonstrate a close link between sleep/circadian functioning and BD suggesting that a disruption in the sleep and circadian systems is a vital component of BD. A more integrated consideration of sleep disruption in BD will result in a clearer understanding of the broader symptoms in mood episodes and across the lifespan. This may be particularly true for emotional processing and certain cognitive domains where there are similar associations between sleep disruption and BD as reviewed below. However there are very few studies that have directly examined the relationship between sleep and cognition or sleep and emotional processing in BD.

Overlapping Cognitive Processing Deficits Involving the Prefrontal Cortex in Bipolar and Following Sleep Deprivation

BD and sleep deprivation both lead to deficits in many cognitive domains reliant upon adequate PFC functioning including response inhibition, higher order attention processes, working memory, and episodic learning/memory (Bearden et al., 2001; Boonstra, Stins, Daffertshofer, & Beek, 2007; Bora et al., 2009; K. Jones & Harrison, 2001; Muzur, Pace-Schott, & Hobson, 2002). While cognitive deficits are most severe during a mood episode in BD (Kurtz & Gerraty, 2009), there is a growing body of evidence suggesting that cognitive impairment persists during periods of remission or euthymia (Mann-Wrobel, Carreno, & Dickinson, 2011; Robinson & Ferrier, 2006; Torres et al., 2007). Studies of euthymic BD patients have found medium to large effect sizes for cognitive impairment, which some have argued reflects a trait-like deficit in certain types of information processing, especially PFC-mediated cognitive operations (Bora et al., 2009). Further, those patients with the greatest cognitive impairment have the poorest social and vocational functioning (Atre-Vaidya et al., 1998; Bearden et al., 2011; Jaeger, Berns, Loftus, Gonzalez, & Czobor, 2007; Martinez-Arán et al., 2004) and patients whose cognition improves demonstrate an improvement in vocational functioning (Bearden et al., 2011) suggesting that cognitive processing deficits may be an important treatment target. Similarly, when healthy people are deprived of sleep, studies report deficits ranging from the most basic (e.g., alertness and vigilance) to the most advanced cognitive abilities (e.g., decision making and problem solving; McCoy & Strecker, in press). However, the PFC, specifically, has been implicated as an vital brain region underlying many of the observed higher-order cognitive changes (Couyoumdjian et al., 2010; Gosselin, De Koninck, & Campbell, 2005; Harrison & Horne, 1998; Killgore, Lipizzi, Kamimori, & Balkin, 2007; McKenna, Dickinson, Orff, & Drummond, 2007; J. Nilsson et al., 2005). In addition to these tasks of higher-order cognitive functions, performance decrements in vigilance tasks have also been observed (Belenky et al., 2003; Dinges et al., 1997; Jewett, Dijk, Kronauer, & Dinges, 1999) along with reduced ability to identify odors (Killgore & McBride, 2006), abilities subserved by the dorsolateral and orbitofrontal PFC, respectively. Furthermore, the PFC shows the greatest change from waking to sleep (Braun et al., 1997), characterized by reduced activity during NREM sleep in the PFC (Maquet, 2000), with the exception of selective reactivation in regions of the medial PFC (Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Within REM sleep many cortical areas increase activation to similar levels seen during wake (Maquet et al., 1990). However, the PFC (specifically dorsolateral PFC) remains deactivated in REM sleep (Maquet et al., 2000; Maquet et al., 2005). Upon waking, PFC regions lag behind other cortical areas in achieving waking levels of activation (Nofzinger et al., 1997) suggesting the PFC is sensitive to sleep/circadian disruption. Below, we systematically reviewed results from neuroimaging studies of both euthymic BD patients and young non-mentally ill sleep deprived participants that focused on cognitive processes reliant upon PFC function in order to draw parallels between the impact of BD and sleep in PFC-mediated operations.

Prefrontal Cognitive Functional Changes during Euthymia

Functional abnormalities of the PFC have been observed in BD and are thought to underlie the cognitive deficits. A recent meta-analysis of functional magnetic resonance imaging (fMRI) studies found that patients with BD exhibited decreased activation compared to healthy controls in brain regions normally activated on cognitive challenges during euthymia. The most prominent region demonstrating decreased activation is in the ventrolateral PFC, which underlies the ability to inhibit a prepotent response (Chen et al., 2011). Table 1 provides a summary of neuroimaging studies examining PFC function and cognition in adult euthymic BD patients. The most consistent change in function is a decreased brain response in the dorsolateral and ventrolateral PFC regions on tasks of working memory and inhibition/selective attention. Interestingly, these neuronal changes are not always accompanied by observed behavioral decrements, though by increasing task difficulty you can often elicit a deficit in euthymic BD patients. This suggests that abnormal PFC response may be a more sensitive trait marker of BD than behavioral performance. While there is a general pattern of decrease brain response in dorsolateral and ventrolateral PFC, this is not always the case. The variable direction of effects suggests that other factors are likely moderating the activation pattern such as medication, age, duration of illness, and potentially sleep/circadian dysfunction. Use of psychotropic medication, in particular, has been shown to influence brain response. Studies of euthymic patients often include samples where the majority of patients are medicated with mood stabilizers such as lithium or anti-psychotic medication, but also include un-medicated euthymic patients (see table 1). While medication effects on BD performance and brain response are not fully understood, studies that have examined the effect have found an increased neuronal response in PFC regions with activity patterns similar to non-medicated healthy comparison participants (Altshuler et al., 2005; Blumberg et al., 2003; Kronhaus et al., 2006), though some studies have also reported no differences (Blumberg et al., 2005; Gruber, Rogowska, & Yurgelun-Todd, 2004; Yurgelun-Todd et al., 2000). Studies that do not find differences suffer from small samples sizes making interpretation of a non-effect difficult. For a complete review of the issue of medication in neuroimaging studies of BD please refer to Phillips and colleagues (2008).

Prefrontal Cognitive Functional Changes during Sleep Deprivation

Table 2 presents the findings from neuroimaging studies of PFC and cognitive functioning in the sleep deprivation literature in young healthy individuals. Generally, studies find reduced cognitive function with reduced neuronal activation following sleep loss in the dorsolateral and ventrolateral PFC for tests of working memory, sustained attention, and response inhibition. Alternatively, increases in neuronal activation in the ventrolateral PFC have been observed during tests of logical reasoning, divided attention, and verbal learning. Notably, some studies have also reported preserved cognitive performances in these latter domains following sleep deprivation making the argument for compensatory neuronal recruitment required to sustain cognitive performance in the face of sleep loss (Drummond, Brown, Salamat, & Gillin, 2004). However, this concept has not been fully explored across cognitive domains as most studies utilizing neuroimaging techniques have focused on working memory, since this cognitive construct is involved in many other cognitive operations. A recent meta-analysis found that sleep deprivation adversely affects both accuracy and reaction time during working memory tasks, with effect sizes generally in the moderate range (Lim & Dinges, 2011). The reader is directed to this meta-analysis for a review of other non-PFC cognitive processes that are impacted by sleep loss. Interestingly, when working memory response time and scanning efficiency processes are separated mathematically the only decrement lies in the response time component (Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). This suggests that attentional decrements (especially those mediated by dorsolateral PFC) may be the most robust impairment following sleep loss rather than cognitive manipulation per se.

Vulnerability and Resiliency to Sleep Disruption

Another aim of many sleep researchers is to identify individuals that are susceptible or resilient to the effects of sleep loss. Studies have primarily used statistical methodologies to look at within session (e.g., well-rested vs. sleep deprived) behavioral performance (Van Dongen, Baynard, Maislin, & Dinges, 2004; Van Dongen, Bender, & Dinges, 2012) and/or biomarkers of resiliency using functional MRI (Chee et al., 2006; Lim, Choo, & Chee, 2007; Tucker et al., 2011). These findings generally are able to separate groups post hoc based upon performance, though identifying reliable *a priori* predictor variables is needed. Studies of circadian phase and timing have found alterations in cognition that may account for some within-subject variability (Van Dongen et al., 2012). For example, a recent study found that polymorphisms on the Period Homologue 3 (Per3) circadian gene affected working memory and attention following sleep loss (Dijk & Archer, 2010), and low-intensity blue and green light interacted with Per3 genotype to alter brain response in ventrolateral and dorsolateral PFC when administered in the morning after a normal vs. sleep deprived night on a working memory task (Vandewalle et al., 2011). These studies indicate that light acts as an activating agent in individuals whose brain function is jeopardized by an adverse circadian phase (Process C) and high homeostatic sleep pressure (Process S).

Summary of Overlapping Cognitive Processing Deficits

Both BD and sleep disruption cause cognitive deficits in PFC-mediated cognitive operations such as response inhibition, higher order attention processes, and working memory. Considering the importance of sleep and circadian functioning in BD, the similarities in the cognitive deficits suggest that sleep likely plays an important role in the cognitive sequelae of BD. The PFC demonstrates structural and functional changes in BD patients, a brain area which is further disrupted in sleep deprivation studies. For example, as reviewed above, decreased activation of the PFC related to attentional requirements of tasks have been observed in sleep deprivation studies (Lim & Dinges, 2011). The specific deficit of PFC top-down attentional modulation is consistent with PFC dysfunction observed in BD where response inhibition and sustained attention are possible endophenotypes of the disorder (Bora et al., 2009). In addition, similar to inhibitory problems observed in BD patients, when healthy controls are deprived of sleep they demonstrate an impaired ability to inhibit a prepotent response (Drummond, Paulus, & Tapert, 2006). This suggests that neuronal changes to the structure and function of the PFC may lead to trait-like deficits in cognition which are likely moderated by sleep/circadian changes in patients. Such a relationship would lead to varying severity of cognitive deficits due to differences in sleep patterns and aid in explaining the variability of findings within the BD literature. Consistent with this idea is the finding from the sleep literature that healthy participants demonstrate variability in their response to sleep loss both in brain activity and behavior such that some individuals do well after sleep loss and others show large deficits (Frey, Badia, & Wright, 2004; Leproult et al., 2003; Van Dongen et al., 2004). Theoretically then, BD patients may possess certain trait-like characteristics in their sleep and circadian function that predispose them to be especially sensitive to sleep and circadian disruption resulting in impaired cognition. Furthermore, within euthymic states, the observed disruption in sleep architecture and circadian dysfunction in BD alters the timing, quality, and quantity of SWS and REM processes. As such, the functional PFC deficits observed in BD are likely, in part, due to the sleep changes in patients given the importance of SWS and REM sleep in cognition (Walker, 2009). If this is true, then studies examining the variability in sleep and circadian architecture and cognitive functioning in BD patients will find a predictive association between the two.

Overlapping Emotional Processing Deficits Involving the Prefrontal Cortex in Bipolar and following Sleep Deprivation

In addition to the dynamic symptom profile in BD which clearly suggests disruption of emotion regulation, there is also evidence to suggest that, even during euthymia, individuals with BD have difficulty with emotional processing resulting from a disconnect of PFC and limbic regions (Green, Cahill, & Malhi, 2007). Similarly, sleep deprivation is commonly found to increase irritability, affective volatility, and increase emotional disturbance/reactivity (Dinges et al., 1997; Horne, 1985; Killgore, 2010). For example, Zohar and colleagues found sleep deprivation in medical residents amplified negative emotional consequences of disruptive daytime events while blunting the positive benefit associated with rewarding activities (Zohar, Tzischinsky, Epstein, & Lavie, 2005), similar to emotional processes observed in BD. Interestingly, sleep loss also appears to bring about an elevation of several dimensions of clinical mood problems and symptoms of psychopathology including elevations in subjective depression, anxiety, paranoia, and somatic complaints (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007).

Prefrontal Emotional Processing Changes during Euthymia

Studies utilizing facial emotion perception paradigms have generally demonstrated that euthymic BD patients have deficits in labeling facial emotions (Getz, Shear, & Strakowski, 2003; Lembke & Ketter, 2002; McClure, Pope, Hoberman, Pine, & Leibenluft, 2003) along with facial affect matching (Addington & Addington, 1998; Bozikas, Tonia, Fokas, Karavatos, & Kosmidis, 2006), though this is not always the case (see Green et al., 2007 for a review). Euthymic BD patients also seem to have impairments in recognition of emotions (Bozikas et al., 2006; Hoernagl et al., 2011). Abnormal emotion processing in euthymic periods is also evident in studies utilizing emotional Stroop tasks where patients have slowed responses to color-naming of depression-related words (French, Richards, & Scholfield, 1996; Kerr, Scott, & Phillips, 2005; Lyon, Startup, & Bentall, 1999), and in affective go/no-go tasks where patients have poor inhibition of emotional material (Murphy et al., 1999). The emotion regulation deficits observed in periods of clinical remission suggest a trait-like deficit in emotional processing (Gopin et al., 2011), that seems to stem from a weakened connection from the medial PFC and limbic regions in the brain (Perlman et al., 2012; Pompei, Jogia et al., 2011). While functional underactivity in BD relative to controls is usually observed in neural systems underlying cognition, the opposite pattern is observed in limbic systems. Medial temporal regions (parahippocampal gyrus and amygdala) and basal ganglia regions (putamen and pallidum) have been consistently observed to show increased activation relative to controls regardless of mood state (Chen et al., 2011; Phillips, Drevets, Rauch, & Lane, 2003a, 2003b). Table 1 highlights studies of euthymic BD patients that demonstrate an abnormally increased response in the medial and orbitofrontal PFC regions in tasks involving emotional processing components. Evidence from neuroimaging studies have demonstrated that cognitive control of emotion in healthy individuals relies upon inhibitory control by many regions within the PFC including orbitofrontal, medial, and dorsolateral regions (in addition to anterior cingulate gyrus). These areas act upon limbic regions within the brain responsible for processing emotional material (Beauregard, Levesque, & Bourgouin, 2001; Green et al., 2007; Keightley et al., 2003; Ochsner et al., 2004). Specifically, during emotion regulation, these PFC regions modulate activity in the amygdala, anterior insula, and striatum. In addition, detailed evaluation of contextual significance of emotional stimuli is undertaken via connectivity between para-limbic memory and dorsolateral PFC attentional systems (LeDoux, 2000).

Prefrontal Emotional Processing Changes during Sleep Deprivation

Despite substantial research efforts into understanding sleep's role in cognition there has been little focus on sleep and circadian impact on basic affective and emotion regulation. This is surprising considering the close link between sleep and psychopathology. Nevertheless, there are a number of recent studies that evaluate both subjective and objective measures of mood and emotional processing that offer an emerging understanding for the critical role of sleep in regulating emotional brain function reliant upon adequate PFC functioning in controlling limbic structures in a top-down manner. For example, evaluation of emotional stimuli is affected by sleep deprivation (Tempesta et al., 2010), as well as the ability to appreciate humor (Killgore, McBride, Killgore, & Balkin, 2006). Further, declines in perceived emotional intelligence (Killgore, Kahn-Greene et al., 2007), which involves self-awareness, interpersonal skills, and adaptive coping skills, are evident when individuals are sleep deprived. When examining the neural processes underlying emotional reactivity that change following sleep loss, studies have found altered PFC-amygdala connections using functional MRI (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Specifically, there is an amplified hyperlimbic reaction in the amygdala in response to negative emotional stimuli following one night of sleep loss. This altered magnitude of limbic activity is associated with a loss of functional connectivity with the medial PFC implying a failure of top-down inhibition on amygdala function within the PFC. More recently, a study also found that sleep loss amplifies reactivity throughout the mesolimbic reward brain networks in response to pleasure-evoking stimuli (Gujar, Yoo, Hu, & Walker, 2011). Further, the amplified reactivity was associated with increased functional connectivity between primary visual processing pathways and limbic regions along with a reduction in coupling of ventrolateral and orbitofrontal PFC regions. Thus, it seems that sleep may be important in maintaining the functional integrity of the PFC circuit with limbic and sensory regions. This is concordant with emerging evidence that one critical function of sleep may be to optimize neuronal connectivity (Krueger et al., 2008). Indeed, sleep deprivation causes decreased functional connectivity in resting state default mode networks (De Havas, Parimal, Soon, & Chee, 2012).

Summary of Overlapping Emotional Processing Deficits

Research consistently finds deficits in emotional processing in BD and more recent studies have begun to highlight similar findings when healthy individuals are deprived of sleep. Neuroimaging BD studies have demonstrated an increase in activity in limbic structures during euthymia (Phillips et al., 2003a, 2003b). This parallels the sleep literature, which has demonstrated hyperactivity in the amygdala in response to negative emotional stimuli following sleep loss (Gujar et al., 2011; Yoo et al., 2007). Considering the strong reciprocal connection between limbic areas and the PFC, researchers in both BD and sleep fields have examined and found changes in functional connectivity implying a failure of top-down inhibition from the PFC. This finding is interesting in the context of BD where there seems to be a disruption of the PFC and associated emotional regulatory systems. It seems that sleep may play an important role in maintaining the functional integrity of this circuit and thus govern appropriate social behavioral repertoires (e.g., optimal social judgments and rational decision making), an area often lacking in BD patients. Thus, those BD patients with more disrupted sleep and circadian functioning compared to other patients would have the most affective processing deficits and associated abnormal brain response. Future studies are encouraged to examine this theoretical link.

Overlapping Neurotransmission and Genetics

Studies that have begun to examine multiple candidate genes and atypical neurotransmitter release which overlap between BD and sleep/circadian function offer possible

neurobiological markers of trait-like characteristics that predispose BD patients to sleep and circadian disruption. For example, dopaminergic and serotonergic pathways (similar pathways that control sleep and circadian functioning) are disrupted in BD (Berk et al., 2007; Cousins, Butts, & Young, 2009; Lima et al., 2008; Oquendo et al., 2007). This has led researchers to develop and test models of dopaminergic and serotonergic neurotransmitter systems affecting both biological rhythms and BD (Harvey, Murray, Chandler, & Soehner, 2010). Additionally, there have been several genes associated with both sleep/circadian functioning and BD, although results have been inconsistent (Kripke, Nievergelt, Joo, Shekhtman, & Kelsoe, 2009). The most consistent findings involve the genes circadian locomotor output cycles kaput (CLOCK) and Per3. Mice studies looking at a mutation of the circadian CLOCK gene show a decrease need for sleep, increased motor activity, lower anxiety, and increased preference for cocaine intake – similar behaviors to patients in a manic episode. Further, these effects are ameliorated with lithium treatment (Roybal et al., 2007). In humans, a single nucleotide polymorphism in the 3' flanking region of CLOCK has been associated with increased evening activity, delayed sleep onset, and less sleep in BD patients (Benedetti et al., 2007). Additional research has shown this polymorphism to be associated with high rates of insomnia, recurrence of illness episodes, and changes in neuronal response in BD patients (Benedetti, Radaelli et al., 2008; Benedetti et al., 2003). Recently, the long allele variant of Per3 clock gene (Per3^{5/5}) has been linked to early onset of BD and the short allele variant Per3^{4/4} with later onset (Benedetti, Dallaspesza et al., 2008). In healthy individuals, Per3^{5/5} is associated with extreme morning chronotypes, whereas Per3^{4/4} is associated with extreme evening chronotypes and delayed sleep phase syndrome (Archer et al., 2003; Dijk & Archer, 2010; K. Jones et al., 2007). Furthermore, each short and long allele variant leads to differences in homeostatic processes and sleep architecture. Per3^{5/5} is associated with more rapid sleep onset (thus increased pressure to sleep), a longer time in SWS during sleep, and increases in theta and alpha activity in wake. Importantly, individuals with Per3^{5/5} perform poorly on cognitive tasks of working memory and attention following extended periods of wakefulness (Dijk & Archer, 2010). However, it should be noted that genetic effects are probabilistic and the phenotype expressed by an individual is dependent upon gene by gene and gene by environmental factor interactions.

Models of a Prefrontal – Limbic Function in Bipolar and Sleep

Models of Cognitive and Emotional processing changes in Bipolar

One popular explanation of why BD produces emotion dysregulation suggests that the known neuropsychological deficits in memory and executive functioning across manic, depressed, and euthymic states lead to an inability to effectively implement specific types of emotion regulation strategies (Green et al., 2007). For example, within BD patients the observed changes in the dorsolateral PFC and anterior cingulate have been implicated in impaired cognitive control and self-monitoring leading to intrusions of affective material (Kerr et al., 2005; Lawrence et al., 2004; Malhi et al., 2004; Murphy et al., 1999; Yurgelun-Todd et al., 2000). Additionally, impairment of the dorsolateral PFC has been implicated in impaired working memory and executive control leading to poor modulation of attention to emotionally salient stimuli (Kerr et al., 2005; Lyon et al., 1999; Murphy et al., 1999). Thus, it seems that impaired cognitive control of the emotional processing system may lead to emotion dysregulation. In light of the strong reciprocal connections between cognitive and emotion neural systems, several researchers have proposed neurobiological theories of BD that include functional and structural abnormalities in fronto-limbic circuits. One model proposes that the diminished PFC modulation of subcortical and medial temporal areas results in dysregulation of mood (Strakowski, Adler, Holland, Mills, & DelBello, 2004; Strakowski, Adler et al., 2005; Strakowski, DelBello, & Adler, 2005). A second model focuses on the interaction between bottom-up emotional appraisal and top-down cognitive control processes centered on subcortical affective appraisal systems (amygdala, basal

ganglia) and PFC and cingulate systems, respectively (Ochsner & Gross, 2005, 2007; Ochsner et al., 2004). Another model of PFC-subcortical connections describes a neural model of emotional circuitry comprising two systems: 1) a ventral system including the amygdala, insula, ventrolateral striatum, ventral regions of the anterior cingulate cortex, and ventral regions of the PFC including medial (ventral aspect of the medial PFC) and orbitofrontal cortex responsible for processing emotionally salient information; and 2) a dorsal system including the hippocampus, dorsal regions of the anterior cingulate cortex, and dorsolateral PFC required for cognitive processing and voluntary regulation of the emotion. This model suggests that overactivation in the ventral system and underactivation in the dorsal system may underlie the neurobiology of BD (Phillips et al., 2003b; Phillips, Ladouceur, & Drevets, 2008). These models share the common theme of a disconnect between top-down control mechanisms in a dorsal PFC system and bottom-up mechanisms in ventral PFC and subcortical regions. Considering the close ties that sleep has with the fronto-limbic system, sleep and circadian disruption are likely to play an important moderating role in the degree of deficits in cognitive and affective processing among individuals with BD.

Inclusion of Sleep Disruption into Bipolar Models of a Prefrontal – Limbic Function in BD

Models of PFC-limbic connections provide a valuable framework in which to examine the neurodevelopment of BD and to help identify biomarkers that represent risk for the disorder. Interestingly, recent research in the sleep literature have begun to develop similar models based upon results in healthy individuals who are sleep deprived such that there is a hyperactive response to emotional material in ventral PFC and subcortical regions and a hypoactive response in dorsal PFC regions in cognitive domains impacted in BD (e.g., vigilance, inhibition, working memory). This has led some to propose that sleep may be important in maintaining the functional integrity the PFC circuit with limbic regions (Krueger et al., 2008; Walker, 2009; Yoo et al., 2007). These similarities in findings are striking and, considering the importance of sleep/circadian rhythms in BD, highlight the need to more closely examine the interaction between sleep/circadian rhythms in the cognitive and affective sequelae of BD. Model development in BD would benefit from incorporating a sleep component into current models to provide the theoretical framework in which to test sleep mechanisms in BD. We suggest that incorporation of sleep would happen at the neural level in maintaining the integrity of the PFC-limbic circuit such that sleep deprived euthymic BD patients are especially vulnerable to greater cognitive/emotional processing impairment and subsequent mood episodes due to an attenuation in this connection. Indeed, the literature would suggest this is the case (Harvey et al., 2010). Further, disruption of sleep and circadian rhythms influence all aspects of neural and neuroendocrine function and the sleep and circadian system is itself regulated across different brain regions and by a range of neurotransmitters (Reghunandanan & Reghunandanan, 2006). Therefore, sleep and circadian disruption likely impacts cognitive/emotional processing and everyday functioning in patients through reciprocal links with brain function. However, it is important to note that BD and sleep both affect many systems in the body outside the brain including cardiovascular and auto-immune systems. A multi-systems approach would aid in explaining the variability in BD symptoms and functioning, including the role of sleep/circadian rhythms in BD (Leboyer et al., 2012). Additionally, sleep and circadian rhythms are entrained to a normal cycle through *zeitgebers* such as light exposure and social rhythms, which include the timing of daily activities. The reciprocal connections between *zeitgebers* and sleep/circadian disruption reflects a cyclical pattern that can happen in individuals where more disruption to the light exposure and social rhythms causes more disruption to the biological rhythms and sleep, which in turn, causes more disruption to light exposure and social rhythms. While no study has directly examined the mechanistic role of sleep in the cognitive and affective deficits seen in BD such as

moderator versus mediator effects, a recent study provides some preliminary evidence. Giglio and colleagues found that everyday functional impairment in interepisode BD patients was mediated through circadian rhythm disturbance (Giglio, Magalhães, Kapczinski, Walz, & Kapczinski, 2010). Further, a subset of subjects received one measure of executive functioning and both constructs were correlated with this measure such that those patients with worse executive functioning had more circadian disturbance and functional impairment. Figure 2 provides an example of an additive model building upon Phillips and colleagues model development work (2008) such that BD changes the dorsal – ventral system and the addition of sleep / circadian disruption with BD leads to greater changes to this pathway than BD alone. Consistent with both BD and sleep literatures, the dorsal system becomes hypoactive and this system's top-down connection with the ventral system is weakened; whereas, the ventral system becomes hyperactive exerting greater bottom-up connectivity to the dorsal system. This figure outlines one possible mechanism by which sleep may interact with BD at the neuronal level highlighting the role of the PFC. We encourage researchers to develop and test more sophisticated models of moderation and mediation effects of sleep and circadian rhythms within the cognitive and affective sequelae of BD.

Conclusions

Sleep and circadian disruption is a core feature of BD and there is increasing evidence for a mechanistic overlap between the neuropathology of BD and the basic control mechanisms of sleep and circadian timing. Considering that sleep/circadian disruption is one of the most commonly reported signs that precede a mood episode (e.g., depression or mania), an individual's sleep biology may prove to be useful in the identification of biological markers of the disease progression. Independent literatures have begun to demonstrate that 1) patients with BD in euthymic states have PFC-mediated cognitive and emotional processing deficits, 2) sleep plays a crucial role in cognitive and emotional operations in healthy individuals through PFC neural systems, and 3) BD patients demonstrate impairments in their circadian and sleep systems. Given these findings it is unfortunate that more research has not been conducted to examine the role of sleep/circadian function in cognitive and affective processing or research into the sleep/circadian disruption as a marker for the early detection and intervention in BD. The latter may prove important given the more recent studies that have demonstrated the efficacy of sleep and circadian rhythms as treatment targets (Frank et al., 2005; Frank, Swartz, & Kupfer, 2000). Based upon the current literature reviewed here, we propose that a more integrated consideration of sleep disruption in the neural models of cognitive and affective processing in BD will result in a clearer understanding of the broader health problems that are associated with the illness and aid in explaining some of the mixed findings within the BD literature. For example, studies do not always consistently find decreased activation on cognitive tasks and increased activation on affective tasks. Furthermore, application of this information to clinical practice could substantially improve the quality of life and everyday functioning of patients, even during periods of "clinical remission."

References

- Addington J, Addington D. Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schizophr Res.* 1998; 32:171–181. [PubMed: 9720122]
- Adler C, Holland S, Schmithorst V, Tuchfarber M, Strakowski S. Changes in neuronal activation in patients with bipolar disorder during performance of a working memory task. *Bipolar Disorder.* 2004; 6(6):540–549.

- Allin M, Marshall N, Schulze K, Walshe M, Hall M, Picchioni M. A functional MRI study of verbal fluency in adults with bipolar disorder and their unaffected relatives. *Psychological Medicine*. 2010; 40(12):2025–2035. [PubMed: 20146832]
- Altshuler L, Bookheimer S, Townsend J, Proenza M, Eisenberger N, Sabb F. Blunted activation in orbitofrontal cortex during mania: a functional magnetic resonance imaging study. *Biological Psychiatry*. 2005; 58:763–769. [PubMed: 16310510]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th Text Revision. Washington, DC: APA; 2000.
- Ankers D, Jones S. Objective assessment of circadian activity and sleep patterns in individuals at behavioral risk of hypomania. *J Clin Psychol*. 2009; 65:1071–1086. [PubMed: 19670448]
- Archer S, Robilliard D, Skene D, Smits M, Williams A, Arendt J. A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep*. 2003; 26:413–415. [PubMed: 12841365]
- Atre-Vaidya N, Taylor M, Seidenberg M, Reed R, Perrine A, Glick-Oberwise F. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. *Neuropsychiatry*. *Neuropsychol. Behav. Neurol*. 1998; 11:120–126. [PubMed: 9742510]
- Bauer M, Grof P, Rasgon N, Bschor T, Glenn T, Whybrow P. Temporal relation between sleep and mood in patients with bipolar disorder. *Bipolar Disord*. 2006; 8:160–167. [PubMed: 16542186]
- Bearden CE, Hoffman KM, Cannon TD. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disord*. 2001; 3:106. [PubMed: 11465675]
- Bearden CE, Shih VH, Green MF, Gitlin M, Sokolski KN, Levander E. The impact of neurocognitive impairment on occupational recovery of clinically stable patients with bipolar disorder: a prospective study. *Bipolar Disord*. 2011; 13:323–333. [PubMed: 21843272]
- Bearden CE, Woogen M, Glahn DC. Neurocognitive and neuroimaging predictors of clinical outcome in bipolar disorder. *Curr Psychiatry Rep*. 2010; 12:499–504. [PubMed: 20839077]
- Beauregard M, Levesque J, Bourgouin P. Neural correlates of conscious self-regulation of emotion. *J Neurosci*. 2001; 21:1–6.
- Belenky G, Wesensten N, Thorne D, Thomas M, Sing H, Redmond D. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *Journal of Sleep Research*. 2003; 12(1):1–12. [PubMed: 12603781]
- Bell-McGinty S, Habeck C, Hilton H, Rakitin B, Scarmeas N, Zarahn E. Identification and differential vulnerability of a neural network in sleep deprivation. *Cerebral Cortex*. 2004; 14(5):496–502. [PubMed: 15054065]
- Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene *Per3* influences age at onset of bipolar disorder. *Neurosci Lett*. 2008; 445:184–187. [PubMed: 18789374]
- Benedetti F, Dallaspezia S, Fulgosi M, Lorenzi C, Serretti A, Barbini B. Actimetric evidence that CLOCK 3111 T/C SNP influences sleep and activity patterns in patients affected by bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 108:631–635. [PubMed: 17221848]
- Benedetti F, Radaelli D, Bernasconi A, Dallaspezia S, Falini A, Scotti G. Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behav*. 2008; 7:20–25. [PubMed: 17428266]
- Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *Am J Med Genet B Neuropsychiatr Genet*. 2003; 123B:23–26. [PubMed: 14582141]
- Berk M, Dodd S, Kauer-Sant'anna M, Malhi G, Bourin M, Kapczinski F. Dopamine dysregulation syndrome: implications for a dopamine hypothesis of bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007; 116:41–49. [PubMed: 17688462]
- Blumberg H, Donegan N, Sanislow C, Collins S, Lacadie C, Skudlarski P. Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. *Psychopharmacology*. 2005; 183:308–313. [PubMed: 16249909]
- Blumberg H, Leung H, Skudlarski P, Lacadie C, Fredericks C, Harris B. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Archives of General Psychiatry*. 2003; 60:601–609. [PubMed: 12796223]

- Boonstra T, Stins J, Daffertshofer A, Beek P. Effects of sleep deprivation on neural functioning: an integrative review. *Cellular and Molecular Life Sciences*. 2007; 64:934–946. [PubMed: 17347797]
- Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009; 113:1–20. [PubMed: 18684514]
- Bozikas V, Tonia T, Fokas K, Karavatos A, Kosmidis M. Impaired emotion processing in remitted patients with bipolar disorder. *J Affect Disord*. 2006; 91:53–56. [PubMed: 16413611]
- Braun A, Balkin T, Wesenten N, Carson R, Varga M, Baldwin P. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain*. 1997; 120:1173–1197. [PubMed: 9236630]
- Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*. 2000; 12(1):1–47. [PubMed: 10769304]
- Catapano, LA.; Chen, G.; Jing, D.; Zarate, CA., Jr; Manji, HK. Cellular plasticity cascades: genes to behavior pathways in the pathophysiology and treatment of bipolar disorder. In: Charney DS, NE., editor. *Neurobiology of Mental illness*. New York City: Oxford University Press; 2009.
- Chee M, Choo W. Functional imaging of working memory after 24 hr of total sleep deprivation. *Journal of Neuroscience*. 2004; 24(19):4560–4567. [PubMed: 15140927]
- Chee M, Chuah L, Venkatraman V, Chan W, Philip P, Dinges D. Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *NeuroImage*. 2006; 31:419–428. [PubMed: 16427321]
- Chen C-H, Suckling J, Lennox B, Ooi C, Bullmore E. A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord*. 2011; 13:1–15. [PubMed: 21320248]
- Choo W, Lee W, Venkatraman V, Sheu F, Chee M. Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. *Neuroimage*. 2005; 25(2):579–587. [PubMed: 15784437]
- Chuah L, Dolcos F, Chen A, Zheng H, Parimal S, Chee M. Sleep deprivation and interference by emotional distracters. *Sleep*. 2010; 33(10):1305–1313. [PubMed: 21061852]
- Chuah L, Venkatraman V, Dinges D, Chee M. The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *The Journal of Neuroscience*. 2006; 26(27):7156–7162. [PubMed: 16822972]
- Costafreda S, Fu C, Picchioni M, Kane F, McDonald C, Prata D. Increased inferior frontal activation during word generation: a marker of genetic risk for schizophrenia but not bipolar disorder? *Human Brain Mapping*. 2009; 30(10):3287–3298. [PubMed: 19479729]
- Cousins D, Butts K, Young A. The role of dopamine in bipolar disorder. *Bipolar Disord*. 2009; 11:787–806. [PubMed: 19922550]
- Couyoumdjian A, Sdoia S, Tempesta D, Curcio G, Rastellini E, DE Gennaro L. The effects of sleep and sleep deprivation on task-switching performance. *Journal of Sleep Research*. 2010; 19:64–70. [PubMed: 19878450]
- Curtis V, Dixon T, Morris R, Bullmore E, Brammer M, Williams S. Differential frontal activation in schizophrenia and bipolar illness during verbal fluency. *Journal of Affective Disorders*. 2001; 66:111–121. [PubMed: 11578663]
- Curtis V, Thompson J, Seal M, Monks P, Lloyd A, Harrison L. The nature of abnormal language processing in euthymic bipolar I disorder: evidence for a relationship between task demand and prefrontal function. *Bipolar Disorder*. 2007; 9(4):358–369.
- Czeisler, C.; Buxton, O.; Khalsa, S. The human circadian timing system and sleep-wake regulation. In: Kryger, M.; Roth, T.; Dement, W., editors. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier; 2005. p. 375-394.
- D'Esposito M, Postle B, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain and Cognition*. 1999; 41:66–86. [PubMed: 10536086]
- De Havas J, Parimal S, Soon C, Chee M. Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance. *Neuroimage*. 2012; 59(2):1745–1751. [PubMed: 21872664]

- Dijk D, Archer S. PERIOD3, circadian phenotypes, and sleep homeostasis. *Sleep. Med Rev.* 2010; 14:151–160. [PubMed: 19716732]
- Dinges D, Pack F, Williams K, Gillen K, Powell J, Ott G. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep.* 1997; 20(4):267–267. [PubMed: 9231952]
- Drapier D, Surguladze S, Marshall N, Schulze K, Fern A, Hall M. Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. *Biological Psychiatry.* 2008; 64(6):513–520. [PubMed: 18571627]
- Drummond S, Brown G, Gillin J, Stricker J, Wong E, Buxton R. Altered brain response to verbal learning following sleep deprivation. *Nature.* 2000; 403(6770):655–657. [PubMed: 10688201]
- Drummond S, Brown G, Salamat J, Gillin J. Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep.* 2004; 27(3):445–451. [PubMed: 15164897]
- Drummond S, Gillin J, Brown G. Increased cerebral response during a divided attention task following sleep deprivation. *Journal of Sleep Research.* 2001; 10(2):85–92. [PubMed: 11422722]
- Drummond S, Gillin J, Stricker J, Wang E, Brown G. Increased sleepiness after TSD leads to increased activation of the prefrontal cortex as measured with FMRI during a cognitive task. *Sleep.* 1999; 22(Suppl. 1):S326–S327. abstract.
- Drummond S, Paulus M, Tapert S. Effects of two nights sleep deprivation and two nights recovery sleep on response inhibition. *Journal of Sleep Research.* 2006; 15(3):261–265. [PubMed: 16911028]
- Espana R, Scammell T. Sleep neurobiology from a clinical perspective. *Sleep.* 2011; 34:845–853. [PubMed: 21731134]
- Frangou S, Kington J, Raymont V, Shergill S. Examining ventral and dorsal prefrontal function in bipolar disorder: a functional magnetic resonance imaging study. *European Psychiatry.* 2007; 23(4):300–308. [PubMed: 17656073]
- Frank E, Kupfer D, Thase M, Mallinger A, Swartz H, Fagiolini A. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. [*Arch Gen Psychiatry.* 2005; 62:996–1004. [PubMed: 16143731]]
- Frank E, Swartz H, Kupfer D. Interpersonal and social rhythm therapy: Managing the chaos of bipolar disorder. *Biol. Psychiatry.* 2000; 48:593–604. [PubMed: 11018230]
- French C, Richards A, Scholfield E. Hypomania, anxiety, and the emotional stroop. *Br J Clin Psychol.* 1996; 35:617–626. [PubMed: 8955547]
- Frey DJ, Badia P, Wright KP Jr. Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *Journal of Sleep Research.* 2004; 13(4):305–315. [PubMed: 15560765]
- Fuster, J. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe.* Lippincott Williams & Wilkins; 1997.
- Getz G, Shear P, Strakowski S. Facial affect recognition deficits in bipolar disorder. *J Int Neuropsychol Soc.* 2003; 9:623–632. [PubMed: 12755174]
- Giglio L, Magalhães P, Kapczinski N, Walz J, Kapczinski F. Functional impact of biological rhythm disturbance in bipolar disorder. *J Psychiatr Res.* 2010; 44:220–223. [PubMed: 19758600]
- Glahn D, Almasy L, Barguil M, Hare E, Peralta J, Kent JJ. Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch Gen Psychiatry.* 2010; 67:166–177.
- Glahn D, Robinson J, Tordesillas-Gutierrez D, Monkul E, Holmes M, Green M. Fronto-temporal dysregulation in asymptomatic bipolar I patients: a paired associate functional MRI study. *Human Brain Mapping.* 2010; 31(7):1041–1051. [PubMed: 20063304]
- Goldberg, E. *The Executive Brain: Frontal Lobes and the Civilized Mind.* Oxford University Press; 2001.
- Gopin C, Burdick K, DeRosse P, Goldberg T, Malhotra A. Emotional modulation of response inhibition in stable patients with bipolar I disorder: a comparison with healthy and schizophrenia subjects. *Bipolar Disord.* 2011; 13:164–172. [PubMed: 21443570]

- Gosselin A, De Koninck J, Campbell K. Total sleep deprivation and novelty processing: implications for frontal lobe functioning. *Clinical Neurophysiology*. 2005; 116:211–222.
- Green M, Cahill C, Malhi G. The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. *J Affect Disord*. 2007; 103:29–42. [PubMed: 17328959]
- Gruber S, Rogowska J, Yurgelun-Todd D. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. *Journal of Affective Disorders*. 2004; 82(2):191–201. [PubMed: 15488247]
- Gujar N, Yoo S, Hu P, Walker M. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *Journal of Neuroscience*. 2011; 31:4466–4474. [PubMed: 21430147]
- Hamilton L, Altshuler L, Townsend J, Bookheimer S, Phillips O, Fischer J. Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task. *Human Brain Mapping*. 2009; 30(12):3958–3969. [PubMed: 19449330]
- Harrison Y, Horne JA. Sleep loss impairs short and novel language tasks having a prefrontal focus. *Journal of Sleep Research*. 1998; 7(2):95–100. [PubMed: 9682180]
- Harvey A. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry*. 2008; 165:820–829. [PubMed: 18519522]
- Harvey A, Murray G, Chandler R, Soehner A. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. *Clinical Psychology Review*. 2010; 31:225–235.
- Hassel S, Almeida J, Kerr N, Nau S, Ladouceur C, Fissell K. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. *Bipolar Disorder*. 2008; 10(8):916–927.
- Hoernagl C, Muehlbacher M, Biedermann F, Yalcin N, Baumgartner S, Schwitzer G. Facial emotion recognition and its relationship to subjective and functional outcomes in remitted patients with bipolar I disorder. *Bipolar Disorder*. 2011; 13:537–544.
- Horne JA. Sleep function, with particular reference to sleep deprivation. *Annals of Clinical Research*. 1985; 17(5):199–208. [PubMed: 3909914]
- Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. *J Affect Disord*. 2003; 74:209–217. [PubMed: 12738039]
- Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disord*. 2007; 9:93–102. [PubMed: 17391353]
- Jewett M, Dijk D, Kronauer R, Dinges D. Dose-response relationship between sleep duration and human psychomotor vigilance and subjective alertness. *Sleep*. 1999; 22:171–179. [PubMed: 10201061]
- Jogia J, Dima D, Kumari V, Frangou S. Frontopolar cortical inefficiency may underpin reward and working memory dysfunction in bipolar disorder. *World Journal of Biological Psychiatry*. 2011 [Epub ahead of print].
- Jones K, Ellis J, Von Schantz M, Skene D, Dijk D, Archer S. Age-related change in the association between a polymorphism in the PER3 gene and preferred timing of sleep and waking activities. *J Sleep Res*. 2007; 16:12–16. [PubMed: 17309758]
- Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Medicine Review*. 2001; 5:463–475.
- Jones S, Hare D, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disorders*. 2005; 7:176–186. [PubMed: 15762859]
- Kahn-Greene E, Killgore D, Kamimori G, Balkin T, Killgore W. The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Medicine*. 2007; 8(3):215–221. [PubMed: 17368979]
- Kaladjian A, Jeanningros R, Azorin J, Nazarian B, Roth M, Mazzola-Pomietto P. Reduced brain activation in euthymic bipolar patients during response inhibition: an event-related fMRI study. *Psychiatry Research*. 2009; 173(1):45–51. [PubMed: 19442494]

- Keightley M, Winocur G, Graham S, Mayberg H, Hevenor S, Grady C. An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia*. 2003; 41:585–596. [PubMed: 12559151]
- Kerr N, Scott J, Phillips M. Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. *Br J Clin Psychol*. 2005; 44:343–356. [PubMed: 16238881]
- Killgore W. Effects of sleep deprivation on cognition. *Progress in Brain Research*. 2010; 185:105–129. [PubMed: 21075236]
- Killgore W, Kahn-Greene E, Lipizzi E, Newman R, Kamimori G, Balkin T. Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Medicine*. 2007; 9(5):517–526. [PubMed: 17765011]
- Killgore W, Lipizzi E, Kamimori G, Balkin T. Caffeine effects on risky decision making after 75 hours of sleep deprivation. *Aviation, Space, and Environmental Medicine*. 2007; 78(10):957–962.
- Killgore W, McBride S. Odor identification accuracy declines following 24 h of sleep deprivation. *Journal of Sleep Research*. 2006; 15(2):111–116. [PubMed: 16704564]
- Killgore W, McBride S, Killgore D, Balkin T. The effects of caffeine, dextroamphetamine, and modafinil on humor appreciation during sleep deprivation. *Sleep*. 2006; 29(6):841–847. [PubMed: 16796223]
- Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Hum. Mol. Genet*. 2006; 15:R271–R277. [PubMed: 16987893]
- Kripke D, Nievergelt C, Joo E, Shekhtman T, Kelsoe J. Circadian polymorphisms associated with affective disorders. *J Circadian Rhythms*. 2009; 7:2. [PubMed: 19166596]
- Kronhaus D, Lawrence N, Williams A, Frangou S, Brammer M, Williams S. Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. *Bipolar Disorder*. 2006; 8(1):28–39.
- Krueger J, Rector D, Roy S, Van Dongen H, Belenky G, Panksepp J. Sleep as a fundamental property of neuronal assemblies. *Nature Review Neuroscience*. 2008; 9(12):910–919.
- Kurtz M, Gerraty R. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology*. 2009; 23:551–562. [PubMed: 19702409]
- Lagopoulos J, Ivanovski B, Malhi G. An event-related functional MRI study of working memory in euthymic bipolar disorder. *J Psychiatry Neurosci*. 2007; 32:174–184. [PubMed: 17476364]
- Lagopoulos J, Malhi G. A functional magnetic resonance imaging study of emotional Stroop in euthymic bipolar disorder. *Neuroreport*. 2007; 18:1583–1587. [PubMed: 17885606]
- Lawrence N, Williams A, Surguladze S, Giampietro V, Brammer M, Andrew C. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol. Psychiatry*. 2004; 55:578–587. [PubMed: 15013826]
- Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R. Can bipolar disorder be viewed as a multi-system inflammatory disease? *Journal of Affective Disorders*, in press. 2012
- LeDoux J. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000; 23:155–184. [PubMed: 10845062]
- Lembke A, Ketter T. Impaired recognition of facial emotion in mania. *Am J Psychiatry*. 2002; 159:302–304. [PubMed: 11823275]
- Leprout R, Colechia EF, Berardi AM, Stickgold R, Kosslyn SM, Van Cauter E. Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *American Journal of Physiology: Regulatory, Integrative, and Comparative Physiology*. 2003; 284(2):R280–R290.
- Lim J, Choo W, Chee M. Reproducibility of changes in behaviour and fMRI activation associated with sleep deprivation in a working memory task. *Sleep*. 2007; 30:61–70. [PubMed: 17310866]
- Lim J, Dinges D. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull*. 2011; 136:375–389. [PubMed: 20438143]
- Lima M, Andersen M, Reksidler A, Silva A, Zager A, Zanata S. Blockage of dopaminergic D(2) receptors produces decrease of REM but not of slow wave sleep in rats after REM sleep deprivation. *Behav Brain Res*. 2008; 188:406–411. [PubMed: 18201777]

- Lyon H, Startup M, Bentall R. Social cognition and the manic defense: attributions, selective attention, and self-schema in bipolar affective disorder. *J Abnorm Psychol.* 1999; 108:273–282. [PubMed: 10369037]
- Malhi G, Lagopoulos J, Owen A, Ivanovski B, Shnier R, Sachdev P. Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. *Journal of Affective Disorders.* 2007; 97:109–122. [PubMed: 16837058]
- Malhi G, Lagopoulos J, Sachdev P, Ivanovski B, Shnier R, Ketter T. Is a lack of disgust something to fear? A functional magnetic resonance imaging facial emotion recognition study in euthymic bipolar disorder patients. *Bipolar Disorders.* 2007; 9(4):345–357. [PubMed: 17547581]
- Malhi G, Lagopoulos J, Sachdev P, Mitchell P, Ivanovski B, Parker G. Cognitive generation of affect in hypomania: an fMRI study. *Bipolar Disorders.* 2004; 6:271–285. [PubMed: 15225144]
- Malhi G, Lagopoulos J, Sachdev P, Mitchell P, Ivanovski B, Parker G. An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disorders.* 2005; 7:58–69. [PubMed: 16225562]
- Mann-Wrobel M, Carreno J, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord.* 2011; 13:334–342. [PubMed: 21843273]
- Maquet P. Sleep function(s) and cerebral metabolism. *Behav Brain Res.* 1995; 69:75–83. [PubMed: 7546320]
- Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. *Journal of Sleep Research.* 2000; 9(3):207–231. [PubMed: 11012860]
- Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R. Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [18F]2-fluoro-2-deoxy-D-glucose method. *Brain Research.* 1990; 513:136–143. [PubMed: 2350676]
- Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips C. Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience.* 2000; 3(8):831–836.
- Maquet P, Ruby P, Maudoux A, Albouy G, Sterpenich V, Dang-Vu T. Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. *Progress in Brain Research.* 2005; 150:219–227. [PubMed: 16186026]
- Martinez-Arán A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord.* 2004; 6:224. [PubMed: 15117401]
- McClure E, Pope K, Hoberman A, Pine D, Leibenluft E. Facial expression recognition in adolescents with mood and anxiety disorders. *Am J Psychiatry.* 2003; 160:1172–1174. [PubMed: 12777278]
- McCoy J, Strecker R. The cognitive cost of sleep lost. *Neurobiol Learn Mem.* in press.
- McKenna BS, Dickinson DL, Orff HJ, Drummond SP. The effects of one night of sleep deprivation on known-risk and ambiguous-risk decisions. *Journal of Sleep Research.* 2007; 16(3):245–252. [PubMed: 17716272]
- Monks P, Thompson J, Bullmore E, Suckling J, Brammer M, Williams S. A functional MRI study of working memory task in euthymic bipolar disorder: evidence for task-specific dysfunction. *Bipolar Disorder.* 2004; 6:550–564.
- Mu Q, Nahas Z, Johnson K, Yamanaka K, Mishory A, Koola J. Decreased cortical response to verbal working memory following sleep deprivation. *Sleep.* 2005; 28(1):55–67. [PubMed: 15700721]
- Murphy F, Sahakian B, Rubinsztein J, Michael A, Rogers R, Robbins T. Emotional bias and inhibitory control processes in mania and depression. *Psychol Med.* 1999; 29:1307–1321. [PubMed: 10616937]
- Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord.* 2010; 12:459–472. [PubMed: 20712747]
- Muzur A, Pace-Schott E, Hobson J. The prefrontal cortex in sleep. *Trends in Cognitive Science.* 2002; 6:475–481.
- Nilsson J, Soderstrom M, Karlsson A, Lekander M, Akerstedt T, Lindroth N. Less effective executive functioning after one night's sleep deprivation. *Journal of Sleep Research.* 2005; 14(1):1–6. [PubMed: 15743327]
- Nilsson K, Jorgensen C, Craig T, Straarup K, Licht R. Self-esteem in remitted bipolar disorder patients: a meta-analysis. *Bipolar Disord.* 2010; 12:585–592. [PubMed: 20868457]

- Nofzinger E, Mintun M, Wiseman M, Kupfer D, Moore R. Forebrain activation in REM sleep: an FDG PET study. *Brain Research*. 1997; 770:192–201. [PubMed: 9372219]
- Nurnberger JJ, Adkins S, Lahiri D, Mayeda A, Hu K, Lewy A. Melatonin suppression by light in euthymic bipolar and unipolar patients. *Archiv Gen psychiatry*. 2000; 57:572–579.
- Ochsner K, Gross J. The cognitive control of emotion. *Trends in Cognitive Science*. 2005; 9:242–249.
- Ochsner, K.; Gross, J. The neural architecture of emotion regulation. In: Gross, J., editor. *Handbook of Emotion Regulation*. New York: Guilford Press; 2007. p. 87-109.
- Ochsner K, Knierim K, Ludlow D, Hanelin J, Ramachandran T, Glover G. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *J Cogn Neurosci*. 2004; 16:1746–1772. [PubMed: 15701226]
- Ongur D, Ferry A, Price J. Architectonic subdivision of the human orbital and medial prefrontal cortex. *The Journal of Comparative Neurology*. 2003; 460:425–449. [PubMed: 12692859]
- Oquendo M, Hastings R, Huang Y, Simpson N, Ogden R, Hu X. Brain serotonin transporter binding in depressed patients with bipolar disorder using positron emission tomography. *Arch Gen Psychiatry*. 2007; 64:201–208. [PubMed: 17283287]
- Perlman S, Almeida J, Kronhaus D, Versace A, Labarbara E, Klein C. Amygdala activity and prefrontal cortex-amygdala effective connectivity to emerging emotional faces distinguish remitted and depressed mood states in bipolar disorder. *Bipolar Disorders*. 2012; 14(2):162–174. [PubMed: 22420592]
- Petrides, M.; Pandya, D. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Boller, F.; Grafman, J., editors. *Handbook of neuropsychology*. Amsterdam: Elsevier; 1994. p. 17-57.
- Petrides M, Pandya D. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience*. 1999; 11:1011–1036. [PubMed: 10103094]
- Petrides M, Pandya D. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *European Journal of Neuroscience*. 2002:16.
- Phillips M, Drevets W, Rauch S, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biological Psychiatry*. 2003a; 54:504–514. [PubMed: 12946879]
- Phillips M, Drevets W, Rauch S, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biological Psychiatry*. 2003b; 54:515–528. [PubMed: 12946880]
- Phillips M, Ladouceur C, Drevets W. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry*. 2008; 13:833–857.
- Pompei F, Dima D, Rubia K, Kumari V, Frangou S. Dissociable functional connectivity changes during the Stroop task relating to risk, resilience and disease expression in bipolar disorder. *Neuroimage*. 2011; 57(2):576–582. [PubMed: 21570470]
- Pompei F, Jogia J, Tatarelli R, Girardi P, Rubia K, Kumari V. Familial and disease specific abnormalities in the neural correlates of the Stroop Task in Bipolar Disorder. *Neuroimage*. 2011; 56(3):1677–1684. [PubMed: 21352930]
- Reghunandanan V, Reghunandanan R. Neurotransmitters of the suprachiasmatic nuclei. *J Circadian Rhythms*. 2006; 4:2. [PubMed: 16480518]
- Ritter P, Marx C, Bauer M, Lepold K, Pfennig A. The role of disturbed sleep in the early recognition of bipolar disorder: a systematic review. *Bipolar Disorder*. 2011; 13:227–237.
- Robinson J, Bearden C, Monkul E, Tordesillas-Gutiérrez D, Velligan D, Frangou S. Fronto-temporal dysregulation in remitted bipolar patients: an fMRI delayed-non-match-to-sample (DNMS) study. *Bipolar Disorders*. 2009; 11(4):351–360. [PubMed: 19500088]
- Robinson J, Ferrier I. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disorder*. 2006; 8:103.
- Robinson J, Monkul E, Tordesillas-Gutiérrez D, Franklin C, Bearden C, Fox P. Fronto-limbic circuitry in euthymic bipolar disorder: evidence for prefrontal hyperactivation. *Psychiatry Research*. 2008; 164(2):106–113. [PubMed: 18930635]

- Roennebert T, Foster R. Twilight times: light and the circadian system. *Photochem Photobiol.* 1997; 66:549–561. [PubMed: 9383985]
- Rolls E, Grabenhorst F. The orbitofrontal cortex and beyond: from affect to decision-making. *Progress in Neurobiology.* 2008; 86(3):216–244. [PubMed: 18824074]
- Roybal K, Theobald D, Graham A, DiNieri J, Russo S, Krishnan V. Mania-like behavior induced by disruption of CLOCK. *Proc Natl Acad Sci U S A.* 2007; 104:6406–6411. [PubMed: 17379666]
- Shneerson, J. *Handbook of Sleep Medicine.* Oxford: Blackwell; 2000.
- Silber M, Ancoli-Israel S, Bonnet M, Chokroverty S, Grigg-Damberger M, Hirshkowitz M. The visual scoring of sleep in adults. *J Clin Sleep Med.* 2007; 3:121–131. [PubMed: 17557422]
- Simon G, Bauer M, Ludman E, Operskalski B, Unutzer J. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. *J Clin Psychiatry.* 2007; 68:1237–1245. [PubMed: 17854249]
- Soshi T, Kuriyama K, Aritake S, Enomoto M, Hida A, Tamura M. Sleep deprivation influences diurnal variation of human time perception with prefrontal activity change: a functional near-infrared spectroscopy study. *PLoS One.* 2010; 5(1):e8395. [PubMed: 20049334]
- Strakowski S, Adler C, Holland S, Mills N, DelBello M. A preliminary fMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology.* 2004; 29:1734–1740. [PubMed: 15173843]
- Strakowski S, Adler C, Holland S, Mills N, DelBello M, Eliassen J. Abnormal fMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. *American Journal of Psychiatry.* 2005; 162:1697–1705. [PubMed: 16135630]
- Strakowski S, DelBello M, Adler C. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry.* 2005; 10:105–116. [PubMed: 15340357]
- Surguladze S, Marshall N, Schulze K, Hall M, Walshe M, Bramon E. Exaggerated neural response to emotional faces in patients with bipolar disorder and their first-degree relatives. *Neuroimage.* 2010; 53(1):58–64. [PubMed: 20595014]
- Tempesta D, Couyoumdjian A, Curcio G, Moroni F, Marzano C, De Gennaro L. Lack of sleep affects the evaluation of emotional stimuli. *Brain Research Bulletin.* 2010; 82:104–108. [PubMed: 20117179]
- Thermenos H, Goldstein J, Milanovic S, Whitfield-Gabrieli S, Makris N, Laviolette P. An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.* 2010; 153B(1):120–131.
- Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R. Neural basis of alertness and cognitive performance impairments during sleepiness: I. Effects of 24 hours of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research.* 2000; 9(4):335–352. [PubMed: 11123521]
- Torres JJ, Boudreau VG, Yatham LN. Neuropsychological deficits in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl.* 2007; 116:17–26. [PubMed: 17688459]
- Tucker A, Rakitin B, Basner R, Gazes Y, Steffener J, Stern Y. fMRI activation during failures to respond key to understanding performance changes with sleep deprivation. *Behavioural Brain Research.* 2011; 218:73–79. [PubMed: 21074577]
- Tucker A, Whitney P, Belenky G, Hinson J, Van Dongen H. Effects of sleep deprivation on dissociated components of executive functioning. *Sleep.* 2010; 33(1):47–51. [PubMed: 20120620]
- Van Dongen H, Baynard M, Maislin G, Dinges D. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep.* 2004; 27(3):423–433. [PubMed: 15164894]
- Van Dongen H, Bender A, Dinges D. Systematic individual differences in sleep homeostatic and circadian rhythm contributions to neurobehavioral impairment during sleep deprivation. *Accident analysis and prevention.* 2012; 45(Suppl):11–16. [PubMed: 22239924]
- Vandewalle G, Archer S, Wuillaume C, Baateau E, Degueldre C, Luxen A. Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *Journal of Biological Rhythms.* 2011; 26(3):249–259. [PubMed: 21628552]

- Venkatraman V, Chuah Y, Huettel S, Chee M. Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. *SLleep*. 2007; 30(5):603–609. [PubMed: 17552375]
- Walker M. The Role of Sleep in Cognition and Emotion. *Ann. N.Y. Acad. Sci.* 2009; 1156:168–197. [PubMed: 19338508]
- Wessa M, Houenou J, Paillere-Martinot M, Berthoz S, Artiges E, Leboyer M. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry*. 2007; 164:638–646. [PubMed: 17403978]
- Wood J, Birmaher B, Axelson D, Ehmann M, Kalas C, Monk K. Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. *Psychiatry Res*. 2009; 166:201–209. [PubMed: 19278733]
- Wulff K, Gatti S, Wettstein J, Foster R. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nature Review Neuroscience*. 2010; 11:589–599.
- Yoo S, Gujar N, Hu P, Jolesz F, Walker M. The human emotional brain without sleep - a prefrontal amygdala disconnect. *Curr Biol*. 2007; 17:R877–R878. [PubMed: 17956744]
- Yurgelun-Todd D, Gruber S, Kanayama G, Killgore W, Baird A, Young A. FMRI during affect discrimination in bipolar affective disorder. *Bipolar Disord*. 2000; 3:237–248. [PubMed: 11249801]
- Zohar D, Tzischinsky O, Epstein R, Lavie P. The effects of sleep loss on medical residents' emotional reactions to work events: a cognitive-energy model. *Sleep*. 2005; 28:47–54. [PubMed: 15700720]

Figure 1. Lateral (left) and medial (right) views of the human brain with subdivisions of the prefrontal cortex discussed in this review colorized.

Figure 2.

Additive model of bipolar disorder and sleep / circadian disruption. The interaction between dorsal and ventral systems is presented for: Left: healthy comparison individuals without bipolar or sleep / circadian disruption; Middle: bipolar patients; and right: bipolar patients who also have sleep and circadian disruption. Thicker black borders and arrows relative to healthy comparison represent increases in brain activation and functional connectivity, respectively. Thinner/dashed borders and smaller arrows relative to healthy comparison represent decreases in brain activation and functional connectivity, respectively

Functional neuroimaging studies of prefrontal response to cognitive and emotional processing tasks in adult euthymic bipolar patients

Table 1

Study	Groups	N Medicated	Groups Matched	Functional Domain	Performance: BPD vs. CON	PFC regions	PFC activity in BPD vs. CON
Curtis et al., 2001	5 BPD, 5 CON	5 BD	Age, IQ	Verbal Fluency	No Differences	Medial PFC	↑
Costafreda et al., 2009	28 BPD, 48 CON	22 BD	Age, IQ, Education	Verbal Fluency	Not Reported	Ventrolateral PFC	↑
Allin et al., 2010	18 BPD, 19 CON	13 BD	Age, Gender, Socio-Economic Status	Verbal Fluency	Decreased in Easier Condition	---	---
Curtis et al., 2007	12 BPD, 12 CON	12 BD	Age, IQ, Education	Language	Decreased Reaction Time	Dorsolateral PFC	↑
Adler et al., 2004	12 BPD, 15 CON	8 BD	Age, Education	Working Memory - maintenance	Decreased	Ventrolateral PFC	↑
Monks et al., 2004	12 BPD, 12 CON	12 BD	Age, IQ, Education	Working Memory - maintenance	No Differences	Anterior PFC	↑
Frangou et al., 2007	7 BPD, 7 CON	7 BD	Age, Gender, Education, IQ	Working Memory - maintenance	No Differences	Dorsolateral PFC	↓
Jogia et al., 2011	36 BPD, 37 CON	36 BD	Age, Gender, IQ	Decision Making	Not Reported	Dorsolateral PFC	↓
Lagopoulos et al., 2007	10 BPD, 10 CON	7 BD	Age, Gender	Working Memory - maintenance	Decreased at the Hardest Difficulty	Medial PFC	↑

Study	Groups	N Medicated	Groups Matched	Functional Domain	Performance: BPD vs. CON	PFC regions	PFC activity in BPD vs. CON
Drapier et al., 2008	20 BPD, 20 CON	16 BD	Age, Gender, Education	Working Memory - maintenance	Decreased at the Hardest Difficulties	Anterior PFC	↑ at easiest condition
Hamilton et al., 2009	21 BPD, 38 CON	17 BD	Age, Gender	Working Memory - maintenance	No Differences	---	---
Robinson et al., 2009	15 BPD, 15 CON	14 BD	Age, Gender, Education	Working Memory - maintenance	No Differences	Dorsolateral PFC	↑
Thermenos et al., 2010	19 BPD, 19 CON	9 BD	Gender, Reading, Parental Education	Working Memory - maintenance	Decreased	Anterior PFC	↑
						Anterior PFC	↓
Glahn et al., 2010	15 BPD, 24 CON	11 BD	Age, Gender, Education	Paired-Association Memory	No Differences	Dorsolateral PFC	↑ for encoding, ↓ for recognition trials
Gruber et al., 2004	11 BPD, 10 CON	8 BD	Education, VIQ, PIQ	Inhibition/Selective Attention	Decreased	Dorsolateral PFC	↑
Strakowski et al., 2005	16 BPD, 16 CON	10 BD	Age, Gender	Inhibition/Selective Attention	Decreased	Ventrolateral PFC	↓
Kronhaus et al., 2006	10 BPD, 11 CON	10 BD	Age	Inhibition/Selective Attention	No Differences	Dorsolateral PFC	↓ deactivations
						Ventrolateral PFC	↓
						Ventrolateral PFC	↓
						Orbitofrontal PFC	↓ deactivations
Pompei et al., 2011	39 BPD, 48 CON	30 BD	Age, Gender, Education, IQ	Inhibition/Selective Attention	No Differences	Ventrolateral PFC	↓
Pompei et al., 2011	39 BPD, 48 CON	30 BD	Age, Gender, Education, IQ	Inhibition/Selective Attention	No Differences	Ventrolateral PFC	↓ connectivity with limbic regions
						Ventrolateral PFC	↓ connectivity with basal ganglia
Kaladjian et al., 2009	20 BPD, 20 CON	19 BD	Age, Gender, Education	Vigilance	No Differences	Anterior PFC	↓
Malhi et al., 2005	12 BPD, 12 CON	8 BD	Age, Gender, Education	Emotional Distractors in Inhibition/Selective Attention	Decreased Reaction Time	Ventrolateral PFC	↓
Lagopoulos and Malhi, 2007	10 BPD, 10 CON	7 BD	Age, Gender, Education	Emotional Distractors in Inhibition/Selective Attention	Not Reported	Ventromedial PFC	↓
						Dorsolateral PFC	↓
Wessa et al., 2007	17 BPD, 17 CON	15 BD	Age, Gender, Education	Emotional Distractors in Vigilance	No Differences	Orbitofrontal PFC	↓ for affective trials during inhibition
Yurgeiun-Todd et al., 2000	14 BPD, 10 CON	14 BD	Not Reported	Identifying Facial Expression	Decreased for Fearful Faces	Dorsolateral PFC	↓ for fear

Study	Groups	N Medicated	Groups Matched	Functional Domain	Performance: BPD vs. CON	PFC regions	PFC activity in BPD vs. CON
Malhi et al., 2007	10 BPD, 10 CON	7 BD	Age, Gender, Education	Identifying Facial Expression	Decreased Reaction Time	Anterior PFC Dorsolateral PFC	↓ for disgust
Malhi et al., 2007	10 BPD, 10 CON	7 BD	Age, Gender	Implicit Affect Generation	No Differences	Dorsolateral PFC Medial PFC	↓ for disgust ↓ for positive and negative affect
Robinson et al., 2008	15 BPD, 16 CON	15 BD	Age, Gender, Parental Education	Matching Facial Emotion	No Differences in Reaction Time	Dorsolateral PFC	↓ for positive and negative affect
Hassel et al., 2008	14 BPD, 24 CON	13 BD	Age, Gender, Reading Ability	Viewing Facial Expression	---	Ventrolateral PFC Dorsolateral PFC	↑
Surguladze et al., 2010	20 BPD, 20 CON	16 BD	Age, Gender, Education	Viewing Facial Expression	---	Medial PFC	↑ for emotional faces

All studies utilized functional magnetic resonance imaging techniques. Grey/White highlights differentiate functional domains. Dashed line delineates cognitive from emotional studies. N = number in sample. BD = Euthymic bipolar patients; CON = Healthy comparison subjects; PFC = prefrontal cortex; ↑ = increase brain response in euthymic bipolar patients relative to healthy comparison subjects; ↓ = decrease brain response in euthymic bipolar patients relative to healthy comparison subjects; --- = no performance change or prefrontal region identified.

Citations: Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004; Allin et al., 2010; Costafreda et al., 2009; Curtis et al., 2001; Curtis et al., 2007; Drapier et al., 2008; Frangou, Kingdon, Raymond, & Shergill, 2007; Glahn et al., 2010; Gruber, Rogowska, & Yurgelun-Todd, 2004; Hamilton et al., 2009; Hassel et al., 2008; Jogia, Dima, Kumari, & Frangou, 2011; Kaladjian et al., 2009; Kronhaus et al., 2006; Lagopoulos, Ivanovski, & Malhi, 2007; Lagopoulos, Owen et al., 2007; Malhi, Lagopoulos, Sachdev et al., 2007; Malhi et al., 2005; Monks et al., 2004; Pompei, Dima, Rubia, Kumari, & Frangou, 2011; Pompei, Jogia et al., 2011; Robinson et al., 2009; Robinson et al., 2008; Strakowski et al., 2005; Surguladze et al., 2010; Thermenos et al., 2010; Wessa et al., 2007; Yurgelun-Todd et al., 2000.

Table 2

Functional neuroimaging studies of prefrontal cortex response to sleep deprivation in healthy individuals

Study	N	Amount of Sleep Loss	Functional Domain	Behavioral Performance following Sleep Loss	PFC regions	PFC activity following Sleep Loss
Drummond et al., 1999	13	35 hours	Working Memory - arithmetic	Decreased	Dorsolateral PFC	↓
Thomas et al., 2000*	17	24 hours	Working Memory - arithmetic	Decreased	All PFC subregions	↓
Habeck et al., 2004	18	48 hours	Working Memory - maintenance	Decreased	Dorsolateral	↓
Chee and Choo, 2004	14	24 hours	Working Memory - maintenance and manipulation	Preserved with increased task complexity	Anterior PFC	↑
Bell-McGinty et al., 2004	19	48 hours	Working Memory - maintenance	Decreased	---	---
Choo et al., 2005	12	24 hours	Working Memory - maintenance	Decreased	Dorsolateral	↓
Mu et al., 2005	20	30 hours	Working Memory - maintenance	Decreased	Ventrolateral PFC	↓
Chee et al., 2006	26	24 & 35 hours	Working Memory - maintenance and manipulation	Similar Decreases at Each Timepoint	Dorsolateral PFC	↓
Tucker et al., 2011	37	48 hours	Failure to Respond during Working Memory	Increased Failure to Respond	Dorsolateral PFC	↓ at each timepoint
Drummond et al., 2000	13	35 hours	Verbal Learning	Free Recall Decreased / Recognition Preserved	Medial PFC	↓
Drummond et al., 2001	13	35 hours	Divided Attention	Preserved	Ventrolateral PFC	↑
Drummond et al., 2004	16	35 hours	Logical Reasoning	Preserved	Dorsolateral PFC	↑
Venkatraman et al., 2007	26	24 hours	Risky Decision Making	No change in risk preference	Ventrolateral PFC	↑
Chuah et al., 2006	27	24 hours	Sustained Attention and Response Inhibition	Decreased with Increased Variability	Orbitofrontal PFC	↓ for decisions involving losses
Soshi et al., 2010**	18	~24 hours	Time Perception	Decreased	Ventrolateral PFC	↓
					Anterior PFC	↓
					Anterior PFC	↑

Study	N	Amount of Sleep Loss	Functional Domain	Behavioral Performance following Sleep Loss	PFC regions	PFC activity following Sleep Loss
Chuah et al., 2010	24	24 hours	Working Memory with Emotional Distractors	Decreased	Dorsolateral PFC	↓ connectivity with amygdala
Yoo et al., 2007	14SD / 12SC	35 hours	Emotional Processing	Not Applicable	Medial PFC	↓ connectivity with amygdala
Gujar et al., 2011	14SD / 13SC	35 hours	Emotional Processing	Positive Bias in Rating Pictures	Medial PFC	↓ connectivity with mesolimbic system
					Orbitofrontal PFC	↓ connectivity with mesolimbic system

All studies utilized functional magnetic resonance imaging techniques unless otherwise noted. Grey/White highlights differentiate functional domains. Dashed line delineates cognitive from emotional studies. N = sample size; SD = sleep deprivation; SC = sleep control; PFC = prefrontal cortex; ↑ = increase brain response following sleep deprivation; ↓ = decrease brain response following sleep deprivation; --- = no prefrontal region identified.

* Positron emission tomography study.

** Near-infrared spectroscopy study.

Citations: Bell-McGinty et al., 2004; Chee & Choo, 2004; Chee et al., 2006; Choo, Lee, Venkatraman, Sheu, & Chee, 2005; LY Chuah et al., 2010; LYM Chuah, Venkatraman, Dinges, & Chee, 2006; Drummond et al., 2000; Drummond, Brown, Salamat, & Gillin, 2004; Drummond et al., 1999; Drummond, Gillin, & Brown, 2001; Gujar, Yoo, Hu, & Walker, 2011; Habeck et al., 2004; Mu et al., 2005; Soshi et al., 2010; Thomas et al., 2000; Tucker et al., 2011; Venkatraman, Chuah, Huettel, & Chee, 2007; Yoo, Gujar, Hu, Jolesz, & Walker, 2007.