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Sleep disturbance and cognitive deficits in bipolar disorder: Toward an integrated examination of disorder maintenance and functional impairment

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HIGHLIGHTS

- We discuss the high prevalence of sleep disruption during the euthymic phase of bipolar disorder.
- Executive functioning, verbal learning and attention deficits persist in the euthymic phase.
- Cognitive deficits in sleep disorders/sleep-deprived subjects are similar to bipolar disorder.
- An integration of sleep and neurocognitive research is proposed.
- Endogenous cognitive endophenotypes and sleep-mediated cognitive endophenotypes may co-exist.

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ABSTRACT

Bipolar disorder is frequently associated with a number of poor outcomes including, but not limited to, a significant impairment in the ability to return to premorbid levels of occupational and psychosocial functioning, often despite the remission of mood symptoms. Sleep disturbance is an oft-reported residual symptom of manic and depressive episodes that has likewise been associated with the onset of manic episodes. Also present during affective episodes as well as the inter-episode periods are reports of deficits in cognitive functioning, which many reports have shown to play an important role in this persistent disability. Despite the presence of deficits in these two domains of functioning during affective episodes as well as the inter-episode phase, there has been no evaluation of the degree to which these systems may interact to maintain such high rates of functional disability. The aim of this review is to examine evidence for the study of the relationship between sleep disturbance and cognitive impairments in bipolar disorder as well as the ways in which deficits in these domains may work together to maintain functional impairment.

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1. Introduction

Bipolar disorder (BD) affects roughly 5.7 million adults in the United States (National Institute of Mental Health Fact Sheet on Bipolar Disorder, 2009) and, according to the World Health Organization, is the sixth leading cause of disability in the world (World Health Organization [WHO], 2006). Functional disability is often prolonged in BD (MacQueen, Young, & Joffe, 2001), suggesting that a focus on both the mechanisms of sustained functional impairment as well as methods of improving functional recovery are most certainly warranted in this population.

Although the majority of functional impairment in BD is associated with affective episodes of depression and/or mania, reports of functional outcomes in BD consistently reveal large percentages of patients who either fail to achieve functional recovery or who demonstrate poor work performance despite subsyndromal mood symptoms (Huxley & Baldessarini, 2007; MacQueen et al., 2001; Zarate, Tohen, Land, & Cavanagh, 2000). The current literature on BD points toward two domains that remain impaired during the inter-episode period despite the return of euthymic mood: sleep and cognitive functioning. There is a growing literature demonstrating persistent sleep problems in euthymic bipolar patients, with one study reporting that the sleep of inter-episode bipolar patients more closely resembled the sleep of insomnia patients than normal controls (Harvey, 2008). These frequent reports of persistently disturbed sleep in the absence of affective symptomatology have led some to suggest that sleep dysregulation is a core mechanism of the illness (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005). Indeed, there is substantial research pointing toward an endogenous circadian rhythm dysfunction in bipolar disorder, with sleep being a key component (Elhers, Frank, & Kupfer, 1988; Mansour, Monk & Nimgaonkar, 2005; Mansour, Wood, et al., 2005). Meanwhile, a number of reports document persistent cognitive deficits during periods of euthymia (Chowdhury, Ferrier, & Thompson, 2003; Ferrier, Stanton, Kelly, & Scott, 1999; Rubinzstein, Michael, Paykel, & Sahakian, 2000), with one study suggesting the most potent predictor of psychosocial outcome is the cognitive domain of verbal memory (Martinez-Àran, Vieta, Colom et al., 2004).

Surprisingly, at the time of this review, there have been no studies conducted that have attempted to assess the degree to which cognitive impairment is associated with disrupted sleep in BD, or whether these two domains may, in a subset of individuals, work together to sustain functional impairment during the inter-episode period. Considering this potentially important gap in the literature, the aims of this review are to: 1) review the current research on sleep disruption during the inter-episode period of BD, 2) review the current research on cognitive deficits in BD during the inter-episode period, 3) discuss associations between sleep and cognitive performance in healthy individuals, 4) integrate the evidence and discuss the possible ways in which sleep disturbance and cognitive deficits may align with current theoretical pathways of functional disability, and 5) propose a targeted line of research to examine these hypothesized mechanisms.

2. Sleep disruption in bipolar disorder

Sleep disturbance is a frequently reported symptom of BD, and, among individuals with insomnia, is associated with a number of poor outcomes including deficits in daytime functioning, increased psychosocial stress, and increases in the utilization of healthcare (Ancoli-Israel & Roth, 1999). Within the context of BD, disrupted sleep has been implicated in the pathogenesis of manic episodes (Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999), and has been shown to serve as one of the early markers of an impending depressive episode (Jackson, Cavanagh, & Scott, 2003). The sleep/wake cycle has been a key component of theoretical conceptualizations of BD that posit that individuals with the disorder may have an underlying genetic diathesis in the form of circadian rhythm instability (Wehr, Sack, & Rosenthal, 1987).

The characteristics of disturbed sleep in BD vary with affective state. Reduced need for sleep is a key criterion in the DSM-IV-TR for a manic episode, whereas both hypersomnia and insomnia may be experienced during depressive episodes (American Psychiatric Association, 2000). Harvey (2008) conducted a comprehensive review of sleep disturbance in the various phases of BD that included 9 studies of sleep disturbance in the manic phase, 10 studies of sleep disturbance in the depressive phase, and 1 study of sleep disturbance in the mixed-mood state. The proportions of individuals experiencing significant sleep disturbance in these samples are uniformly large: 69% to 99% of individuals experienced reduced need for sleep during the manic phase, with more variable rates of hypersomnia (23% to 78%) and insomnia (varying all the way up to 100% of the sample) observed in the depressive phase (Harvey, 2008). There is also a growing literature demonstrating significant impairments in sleep during the inter-episode period. Table 1 details the sample sizes, proportion of participants experiencing a significant sleep disturbance, and main findings of the studies.

2.1. Characteristics of sleep disturbance in the euthymic phase

As evidenced by the percentages in Table 1, sleep disturbance is frequently reported during the inter-episode period, and many individuals in the euthymic phase of BD appear to be much poorer sleepers than healthy individuals. Several studies have reported significant differences in key sleep variables between individuals with BD and healthy controls, giving us a picture, albeit a mixed one at times, of what sleep looks like during the euthymic phase. Millar, Espie, and Scott (2004) conducted an analysis of remitted bipolar patients using both objective and subjective measures of sleep disturbance. One hundred percent of the bipolar sample reported a longstanding sleep disturbance, compared with only 21% in the control group. Analyses of actigraph data revealed trends toward longer total sleep time, longer sleep onset latency, and less efficient sleep among BD participants, as well as significantly more variable sleep duration and night waking time. Subjectively, BD participants reported longer sleep onset latency, as well as greater variability in sleep duration, onset latency and efficiency.

Harvey et al. (2005) conducted a similar analysis, but included a comparison group of individuals with primary insomnia. The authors found that 70% of their bipolar sample experienced a clinically significant sleep disturbance and reported that the sleep of individuals with BD in that study more closely resembled the sleep of individuals with insomnia than of controls. Objective sleep data gathered via actigraphy indicated that individuals with BD had a longer total sleep time as well as lower average daytime activity levels. Subjectively, participants with

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