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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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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.

Keywords

Sleep; Bipolar; Cognitive Deficit; Functional Impairment

Introduction

Bipolar disorder (BD) affects roughly 5.7 million adults in the United States (NIMH; 2011) and, according to the World Health Organization, is the sixth leading cause of disability in the world (WHO; 2006). Functional disability is often prolonged in BD (MacQueen et al., 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 et al., 2007;

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MacQueen et al., 2001, Zarate et al., 2000). The extant 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 et al., 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 et al., 2005). Indeed, there is substantial research pointing toward an endogenous circadian rhythm dysfunction in bipolar disorder, with sleep being a key component (Ehlers, Frank, & Kupfer, 1988; Monsour, Monk & Nimgoankar, 2005a; Monsour et al., 2005b). Meanwhile, a number of reports document persistent cognitive deficits during periods of euthymia (Chowdury et al., 2003; Ferrier et al., 1999; Rubinzstein et al., 2000), with one study suggesting the most potent predictor of psychosocial outcome is the cognitive domain of verbal memory (Martinez-Aran, 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..

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 (Columbo et al., 1999), and has been shown to serve as one of the early markers of an impending depressive episode (Jackson et al., 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 et al., 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 (APA; 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.

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 and colleagues (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 to 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 and colleagues (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 BD reported significantly longer sleep onset latency relative to the good sleeper group. Differences in subjective estimations in sleep variables vs. objective measurements have been fairly consistently reported in the insomnia literature, such that individuals with insomnia tend to underestimate their total sleep time as well as overestimate the time it takes to fall asleep (Carskadon et al., 1976, Mercier et al., 2002). This is an additional similarity the euthymic bipolar group shares with the insomnia group, lending further credence to the conceptualization of BD within the framework of chronic sleep disturbance.

Not all of the data on sleep during the euthymic phase support this conceptualization, however. Jones et al. (2005) conducted an actigraphic assessment of sleep patterns among individuals in the euthymic phase of BD and found no differences on any sleep indices when compared to healthy controls. However, the sample size was small ($n = 19$ per group), and thus analyses may have been underpowered. At the time of the Jones et al. study, the authors reported that only one study had produced results demonstrating sleep disturbance during euthymia, and thus, the null findings were not novel at that time. However, since 2005, there have been three additional studies supporting the presence of significant sleep disturbance in euthymic bipolar individuals, suggesting the Jones et al. null findings may be more of the exception. The authors did find, however, that individuals with BD exhibited less stable and more variable circadian activity patterns, and that this variability was a significant predictor of group status. This variability in comparison to controls is consistent with aforementioned reports of circadian instability among individuals with BD, and suggests that this instability may be a trait marker of the disorder rather than an episode-related phenomenon.

To date, only three studies have examined the sleep architecture of individuals with BD in the euthymic phase. One of the first reports is a 1982 test of the possible overlap of cholinergic mechanisms in depression and REM sleep (Sitaram et al., 1982). The authors found that compared to healthy controls, individuals in the euthymic phase of BD had significantly higher density of eye movements during the first REM period, as well as a significantly higher percentage of REM sleep. Although this study did not examine associations between these variables and prospective mood episodes, other studies utilizing polysomnography have revealed similar patterns of REM density and activity among

patients in the manic phase of illness (Hudson et al., 1988; Hudson et al., 1992) as well as the depressive phase (Lauer et al., 1992). Knowles et al. (1986) did not find the same increased REM percentage and REM density as the Sitaram et al. study; however, they did find more shifts to Stage 1 sleep, awake, and movement time from other stages of sleep when compared to normal controls, suggesting that the sleep of remitted patients was more disrupted than controls.

A more recent study of sleep architecture in remitted BD is consistent with these early findings, and takes the analyses a step further by correlating sleep architecture with prospective mood symptoms. In a sample of 22 individuals in the inter-episode phase of BD and 22 healthy controls, Eidelman and colleagues (2010) found that increased REM density was positively correlated with depressive symptoms, while duration of first REM period as well as percentage of short-wave sleep were positively correlated with manic symptoms. The authors also examined associations between sleep architecture and functional impairment, reporting that REM density and slow wave sleep percentage were positively correlated with impairment, whereas stage 2 sleep percentage was negatively correlated. These findings were largely non-significant in the control group, with only REM density significantly and positively correlating with impairment in the healthy control group. The presence of these abnormalities in sleep architecture during the inter-episode period supports the idea that sleep disturbance may be a trait-marker of BD, with the magnitude of disturbance varying with affective state and intensity of episodes.

Sleep disturbance in euthymia and its relationship to illness course

Sylvia and colleagues (2011) conducted an investigation of sleep disturbance among 483 euthymic individuals selected from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Among these individuals, 15% (72) reported at least a mild sleep disturbance, with this disturbance being more prevalent in individuals who had histories of suicide attempts as well as hypomanic symptoms (Sylvia et al., 2011). Survival analyses revealed a significant association between sleep disturbance and increased risk for mood episode recurrence. Eidelman and colleagues conducted an analysis of sleep disturbance, illness course, and concurrent symptoms among 21 individuals with BD in the euthymic phase. The authors found that a greater number of past depressive episodes was associated with more variable sleep efficiency (a basic ratio of time spent asleep vs. time spent lying in bed), as well as a more variable total wake time.

It is worth noting that while sleep has been identified as a potent prodromal symptom of mood disorders, the possibility that sleep disturbance is also an artifact of affective episodes should also be examined. Sylvia et al. (2011) found that sleep disturbance was associated with a greater number of hypomanic episodes, but that does not mean that sleep disturbance was always the initiating factor. It is possible that greater number of hypomanic episodes is associated with greater sleep disturbance because sleep is markedly *more* disturbed during hypomania, and it may be the case that greater instances of higher magnitude disruption makes it more difficult for an individual to return to stable sleep patterns during the inter-episode period. The same hypothesis can be applied to the Eidelman et al. (2010) findings, as there may be considerable cumulative disruption following higher numbers of past depressive episodes. Thus, it is possible that sleep disturbance and affective episodes exist in a positive feedback loop, with aspects pertaining to the temporal relationship and sequencing of the two varying either on an individual or endophenotypic basis.

Effects of medication and comorbid medical issues on inter-episode sleep

In a largely descriptive analysis, Brill et al. (2011) provided evidence of sleep disturbance in the inter-episode period via a retrospective chart review of 106 individuals in the euthymic

phase of BD. Of those 106 patients, 25 (23.6%) had a clinically significant sleep disturbance consisting of initial insomnia (25%) and middle insomnia (81.25%). Notably, the authors report that the majority of patients who endorsed sleep disturbance endorsed middle insomnia, or sleep continuity disturbance, rather than problems with sleep onset. Disturbed sleep is often associated with medical problems, and individuals with BD are known to be at higher risk of having comorbid medical issues (Kilbourne et al., 2004). Studies of sleep apnea comorbidity have found significantly greater prevalence of apnea among individuals with mood disorders such as depression and BD (Baran & Richert, 2003; Sharafkhaneh et al., 2005), which might possibly be attributed to, among other things, the increased central adiposity, a known sleep apnea risk factor that is also a frequently reported side effect of atypical antipsychotic medications prescribed to individuals with BD. Extending the literature on general functioning among individuals with sleep apnea to individuals with BD may be a line of research worth pursuing in order to shed light on persistent disability in euthymic bipolar phases. Although much of the research on sleep disturbance in BD seems to be geared towards the search for an endogenous mechanism, it would be a mistake to overlook the contribution of sleep-related breathing disorders in this population.

Medication use presents a sizeable roadblock in the study of inter-episode sleep in BD. It is rare that an individual with BD is not being maintained on some form of mood stabilizer, and it is not uncommon for individuals to be taking cocktails of medications including mood stabilizers, antidepressants, anticonvulsants and/or sleep aids. In the Brill et al. (2011) report, approximately 43% of patients were taking medications with sedating effects, leaving room for the possibility that a higher proportion of patients would be endorsing sleep problems were their symptoms not being ameliorated by their medications. Sylvia et al.'s (2011) study did, in fact, explore associations between medications and disrupted sleep, and found that only anticonvulsant medication use predicted sleep disturbance in their sample, though it is unclear as to whether the medication itself is contributing to the sleep disturbances, or if individuals taking this medication represented a comparably more disrupted sample. For example, the majority of participants were taking the anticonvulsant gabapentin, which has sedating effects that are often beneficial to individuals with comorbid insomnia. Thus, much like the Brill et al. report, it is possible that a larger percentage of individuals would have reported sleep problems were they not being successfully treated with pharmacotherapy. The Sylvia et al. report did not give data on whether the medications were selected primarily for their mood stabilizing or sedating properties, thus making this distinction difficult to clarify.

Eidelman and colleagues (2010) paid special attention to the effects of medications on their analyses of sleep architecture in remitted bipolar patients. In their analysis, medications were independently classified based on their known effects on REM, short-wave sleep, or Stage 2 sleep (either no effect, a suppressing effect, or an enhancing effect). In the cases where an individual was taking multiple medications with competing effects (i.e., taking a REM suppressor as well as a REM enhancer), the medications were thought to cancel each other out. The authors found that participants taking a medication that suppressed REM had significantly longer latency to first REM as well as greater REM density. No other medication effects were reported. Thus, there is at least one documented strategy for dealing with the confounding effects of medications on the study of disturbed sleep. More studies that examine medication effects in conjunction with sleep disturbance will help determine if this is a reliable strategy for teasing apart endogenous sleep disturbance from medication-altered sleep disturbance.

Conclusions about sleep in euthymic bipolar disorder

There appears to be a growing literature to support the conceptualization of the inter-episode period of BD as one of chronic sleep disturbance. Numerous studies have reported

significant proportions of clinically significant sleep disturbance, with those numbers likely tempered by medications used to treat insomnia. Studies utilizing polysomnography indicate REM abnormalities during the euthymic phase (namely, increased REM density and greater percentage of REM sleep), whereas actigraphic assessments point toward greater circadian variability and longer sleep onset latency in remitted bipolar patients. Moreover, some of these abnormalities have been associated with prospective depressive and manic symptoms as well as functional impairment.

Neurocognitive Deficits in Bipolar Disorder

There is a considerable literature documenting cognitive deficits in BD that span several domains of neurocognitive functioning including verbal memory, verbal learning, attention, and executive functioning. These deficits have been shown to persist during periods of euthymia, leading some to conceptualize cognitive dysfunction as a core component of a specific endophenotype of BD (Bora et al., 2009). A number of comprehensive reviews and meta-analyses of cognitive functioning in BD have been published within the past decade, and thus, this review will highlight findings from those reports as well as more recent findings from individual studies.

Characteristics of cognitive deficits during euthymia

Broadly, individuals in the inter-episode period of BD tend to exhibit sustained deficits in the domains of executive functioning, verbal learning and memory, and sustained attention. Recently, the executive functioning profile of euthymic BD patients has been found to be roughly the same as individuals with mild cognitive impairments but no history of BD (Osher et al., 2011). This finding builds upon previous research pointing toward consistent deficits in executive functioning during the euthymic period; indeed six exhaustive meta-analyses revealed large effect sizes for tests of executive functioning relative to normal controls (Arts et al., 2008; Bora et al., 2009; Kurtz et al., 2009; Robinson et al., 2006; Torres et al., 2007; Mann-Wrobel et al., 2011). Executive functioning is often an umbrella term that can refer to a broad range of processes including planning, motivation, and inhibition. Robinson et al. (2006) describe their large effect sizes in this realm as not being reflective of a broad dysexecutive syndrome, but as evidence of more selective deficits. The Robinson et al. report revealed large effect sizes for category fluency and mental manipulation (e.g., reverse digit span), medium effect sizes for response inhibition, abstraction, and set shifting, and small effect sizes for verbal fluency by letter. The Arts et al. (2008) analysis reported similar findings, with large effect sizes for executive control (in the Trail Making task), concept shifting (Wisconsin Card Sort perseverative errors), and category fluency, and medium effect sizes for executive control (via the Stroop task).

Importantly, heterogeneity among some of these specific domains of executive functioning, namely executive control, concept shifting, and fluency, was noted in these analyses. Arts et al. refer to three studies that included patients with a higher number of previous psychotic episodes and suggest that the inclusion of those patients may have driven differential findings. Accordingly, research has suggested that greater illness duration, number of episodes, and number of hospitalizations is associated with greater levels of cognitive dysfunction among individuals with BD (Robinson & Ferrier, 2006). Inclusion criteria differed between the Robinson and Arts meta-analyses, and it was evident from both reports that individual definitions of euthymia varied substantially across individual studies. However, regardless of effect size, it certainly appears that executive functions remain disrupted during the euthymic phase.

A 2004 analysis of cognitive deficits in various phases of BD reported that impairments on the Wisconsin Card Sort and the Stroop were apparent among euthymic, manic/hypomanic,

and depressed patients (Martinez-Áran et al., 2004), adding to a line of evidence suggesting certain types of cognitive deficits may persist despite affective recovery, and may comprise a cognitive endophenotype of BD (Bora et al., 2009). Interestingly, inhibitory control was found to be impaired in a sample of euthymic bipolar patients, and was significantly correlated with Tumor Necrosis Factor Alpha (TNF- α) a marker of inflammation that is indicated in the regulation of immune function (Barbosa et al., 2012). Inhibitory control is the single cognitive variable identified as an endophenotype of BD, as it is present in first-degree relatives (Bora et al., 2009). According to Bora et al.'s meta-analysis, set-shifting and verbal memory are also potent contenders for endophenotype status.

Deficits in executive functioning are consistent with neuroanatomical examinations of individuals with BD that have reported abnormalities in the prefrontal cortex (PFC). Reduced neuronal and glial density in the PFC has been reported (Cotter et al., 2002, Öngür et al., 1998, Rajkowska et al., 2001), whereas a functional magnetic resonance imaging (fMRI) study utilizing the Stroop color/word interference task has revealed a trait abnormality in the left ventral PFC (Blumberg et al., 2003). Additional abnormalities may be observed during mood states, which may partially explain why some cognitive deficits are more pronounced during episodes of depression and mania.

Verbal learning and memory deficits are other domains of functioning frequently found to be impaired in individuals with BD, even during periods of euthymic mood. In a 2002 study of euthymic bipolar patients and controls, Cavanagh et al. found that the only significant differences were observed in tests of verbal learning/memory, namely the California Verbal Learning Test (CVLT). These results are mirrored in several meta-analyses of previous studies of cognitive functioning (2008 and earlier), which consistently reported medium to large effect sizes compared to healthy controls (Arts et al., 2008; Robinson et al., 2006). Importantly, the authors discussed the potential overlap between executive functioning and verbal learning, such that executive deficits may affect memory performance, as the CVLT requires a fair amount of organization and set-shifting, which may require the executive system regardless of the test being oriented toward verbal memory. Thus, more research should be conducted to establish whether one or two domains of functioning are reliably impaired in BD. Verbal memory was found to be a predictor of long-term functional outcome in one of the few longitudinal studies conducted on euthymic patients (Bonnín et al., 2010). Indeed, a measure of executive function (the backward digit span from the Wechsler Adult Intelligence Scale) was the only other cognitive variable found to be associated with general as well as occupational functioning at 4-year follow up.

There is mounting evidence to support a sustained attention deficit in BD that persists through periods of euthymia (Bora et al., 2005; Clark & Goodwin, 2004; Liu et al., 2002; Torres et al., 2007). Clark and colleagues (2002) observed impairments in sustained attention even after controlling for any possible interference from mood symptoms. Whereas this effect was associated with chronicity of illness, it was present even in the younger participants who were earlier in their illness course, suggesting that attention deficits may be a trait marker of BD. Indeed, this conceptualization is supported by Bora and colleagues (2009) who included sustained attention deficits as part of a cognitive endophenotype of BD due to findings of the deficit in first-degree relatives.

One of several studies to utilize continuous performance tests (CPT) as a measure of attention, Bora et al. (2006) found that euthymic patients were impaired in their target sensitivity and inconsistent in their response times relative to controls. Although several studies have utilized the CPT to measure sustained attention, there is a high degree of variability of measures in the literature that may temper some of the conclusions that can be drawn about the "purity" of attention deficits in BD. For example, Yates et al (2010) found

that euthymic bipolar participants performed significantly worse than controls on the Digit Span Forward and Digit Span Backward, though these tests are also valid cognitive measures of working memory. The Robinson et al. (2006) meta-analysis includes digit span and trail making in their analyses of attention; however, there is some overlap with attention in these tests of both working memory and executive functioning, respectively. As noted earlier, executive functioning has been identified as one of the most stable cognitive deficits in BD as well as a cognitive endophenotype, leaving the possibility that attention deficits may be better explained by executive function deficits to the extent to which the measure taps both.

Effects of medications on cognitive deficits

As was the case with examining sleep disturbance, medications used to treat BD present a challenge in understanding cognitive deficits in this population. Although medication status was theorized to either mask or contribute to the presence of significant sleep disturbance during periods of euthymia, in the case of cognitive dysfunction, an important question is whether medications are in fact *causing* the problems, either in a direct fashion, or indirectly via the pathway of sleep disturbance.

One of the most commonly prescribed mood stabilizers is lithium, which has several documented adverse cognitive effects such as reduced motor speed, impaired short- and long-term memory, as well as slowed reaction time (Goldberg & Chengappa, 2009). Overall, reports do not suggest that these lithium-induced impairments are necessarily debilitating, with one study suggesting that many of the cognitive deficits shown to be statistically significant were not actually perceptible by the patients themselves (Honig et al., 1999). However, more recent research has blurred the picture somewhat, as a growing number of examinations of cognitive functioning in euthymic individuals have shown no significant differences in performance between lithium takers and non-lithium takers (Altshuler et al., 2004; Arts et al., 2011; López-Jaramillo et al., 2010; O'Shea et al., 2010). Importantly, the non-significant findings regarding lithium were found in studies that examined cognitive functioning in euthymic individuals, thus posing the question of whether some other episode-related variable or interaction was driving the significant associations in other studies.

Second generation or “atypical” antipsychotics have been reported to have negative effects on cognitive functioning. The Arts et al. (2011) report indicated second generation antipsychotic use was associated with reductions in motor speed and basic information processing. However, it is worth noting that this study included individuals with schizoaffective disorder bipolar type as well as bipolar II disorder, leaving open the possibility that the antipsychotics were being prescribed to the more severe individuals, and that illness type and/or severity may have been driving this association. Another study included a comparison group of untreated (drug-free) euthymic patients and found dose-independent deficits on all cognitive tests for the treated bipolar group compared to both control participants as well as the untreated bipolar group, suggesting a direct effect of medication on cognitive functioning (Torrent et al., 2010). Of the antipsychotics used (quetiapine, olanzapine, and risperidone), quetiapine was associated with better performance in verbal learning, short-term memory, and verbal fluency relative to the other medications, suggesting that treatment with this specific antipsychotic may confer the least risk for cognitive side effects.

Relationship between cognitive deficits and functional outcomes

Despite the fact that individuals with BD possess an average of 13 years of education, a striking 55% of these individuals are unemployed (Wingo et al., 2009). This is only one of

many sobering statistics about functional outcomes in BD. There has been considerable research into the factors associated with these poor outcomes, with a growing literature supporting the role of cognitive deficits in occupational and psychosocial functioning despite some mixed findings in earlier studies. The Martinez-Àran et al. study (2007) reported that psychosocial functioning in bipolar patients was associated with neuropsychological measures rather than with clinical variables. No relationship was found between psychosocial functioning and chronicity, total episodes, types of episodes, or numbers of hospitalizations or suicide attempts in their sample. Instead, frontal executive functioning and learning and memory were significantly associated with psychosocial functioning. However, an earlier report using a schizophrenia comparison group found the reverse relationship (Martinez-Àran et al., 2002). Executive functioning in euthymic bipolar patients was found to be similar to the schizophrenic patients, but whereas functional outcome was predicted by negative syndrome and perseverative errors on the Wisconsin Card Sorting task in the schizophrenia group, only general psychopathology was predictive of functional outcome in the bipolar group.

Gilbert et al. (2010) found cognitive variables to be significantly associated with employment trajectory in a sample of 154 patients with BD in the Bipolar Disorder Center for Pennsylvanians. Although the data were collected via self-report, subjective concentration problems were significant predictors of employment status, whereas mood state was non-significant. A more recent report of neurocognitive functioning in euthymic BD utilized more ecologically valid tests to get a better idea of how everyday functioning is impacted by cognitive variables (O'Shea et al., 2010). The tests used were the Test of Everyday Attention (TEA) which includes a subtest that instructs the participant to search for numbers in a mock phone book amidst distractors, the Rivermead Behavioural Memory Test, which includes a task wherein the participant must remember a route the examiner takes walking around a room, and the Behavioral Assessment of the Dysexecutive Syndrome which includes a "zoo maps" task requiring participants to plan a route through a zoo that does not violate a set of rules. Patients performed significantly worse than a healthy control group on the overall scores of all measures. Importantly, although the authors hypothesized no association between cognitive impairment and employment level, the results showed a significant association between impaired attention and unemployment. No significant correlations were found for any mood rating scales and cognitive variables.

It is important to note, however, that associations between mood variables and poor functional outcome do not necessarily exclude the role of cognitive functioning in the development of disability. It is possible that there is a bidirectional effect of poor cognitive functioning and affective symptomatology. For example, a hypothetical individual with bipolar I disorder may experience residual neurocognitive impairment following his index manic episode. Perhaps this impairment made it more difficult for this individual to sustain directed attention, recall verbal information, and carry out complex tasks requiring executive control. These impairments make it more difficult for this man to find a job because even the time and effort required to organize an exhaustive job search is too overwhelming. Continued unemployment leads to feelings of inadequacy, and potentially feelings of hopelessness as well as anxiety about financial security. These symptoms begin to mount until the individual meets criteria for a full-blown episode of major depression, thus making it even more difficult for him to find employment. Thus, although cross-sectional analyses of predictors of poor functional outcomes may point to debilitating mood symptoms, it is distinctly possible that continued cognitive impairment during the euthymic period contributes to the overall outcome.

Cognitive Functioning in Sleep-Deprived Healthy Controls and Patients with Sleep Disorders

In order to consider the potential influence of sleep disturbance on cognitive functioning in BD, we must also examine what is known about the effects of disrupted sleep on cognitive functioning in otherwise healthy individuals. Below, we will review points of convergence and divergence of the literature on cognitive deficits in healthy individuals who have undergone experimental sleep deprivation or who exhibit sleep-disordered breathing vs. individuals with BD.

Cognitive functioning in insomnia and sleep-disordered breathing

Sleep-disordered breathing is a chronic medical condition in which the upper airway is either partially or completely obstructed during sleep. As a result, apneas (suspension of breathing) or hypopneas (shallow breathing or extremely low respiratory rate) result in a reduction of blood oxygenation, causing frequent arousals during sleep. In addition to causing excessive daytime sleepiness, Obstructive Sleep Apnea (OSA), one of the most common forms of sleep-disordered breathing, is also associated with deficits in cognitive functioning and poor work performance (Punjabi & Aurora, 2009) and is thought to affect approximately 2% to 7% of the population in the United States (Punjabi, 2009).

Cognitive functioning in OSA has been given considerable study in the past thirty years, with many studies pointing toward deficits in both attention and executive functioning in affected individuals. Beebe et al. (2003) conducted a meta-analysis of cognitive deficits in OSA, reporting medium to large effect sizes for executive functioning as well as attention/vigilance. This pattern is also seen in children with OSA, with a 2011 study reporting deficits in executive functioning in children aged 7 to 12, deficits that correlated with poor academic functioning relative to controls (Bourke et al., 2011). Impairments in job performance also appear to occur in older adults with the condition, with OSA being associated with self-reported difficulties working due to high levels of daytime sleepiness (Ulfberg et al. 1996).

The evidence is mixed, but some studies report improvement in cognitive functioning following treatment with continuous positive airway pressure (CPAP). Ferini-Strambi et al. (2003) examined cognitive functioning in 23 patients with OSA and 23 normal matched controls prior to treatment with CPAP. Relative to controls, OSA patients were impaired in visuospatial learning, executive function, sustained attention, motor function, motor performance, and constructional abilities. Following 15 days of CPAP, the authors reported improvements in visuospatial learning, attention, and motor performance, while all other cognitive domains remained unaffected. These results did not change after 4 months of treatment. However, an earlier study by Naegel et al. (1998) reported improvements in nearly all cognitive domains including executive functioning, but noted that short-term memory function remained impaired. It is possible that differences in the types of tests used to assess cognitive functioning may partially explain differential findings in these reports. Work performance among individuals with OSA also has been shown to improve following CPAP treatment, with studies reporting improvements in self-perceived work performance, concentration, and task learning, as well as objective improvements in work output (Mulgrew et al., 2007; Ulfberg et al., 1999). However, the fact that improvements following treatment were noted in both studies highlights the effects of disrupted sleep on cognitive functioning.

Cognitive deficits are also well-documented in the insomnia literature. Insomnia is characterized by the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) as difficulty initiating or maintaining sleep or experiencing non-restorative sleep for a period of

at least one month (DSM-IV; APA, 2000). Recent estimates of the prevalence of insomnia vary widely, with numbers ranging from 3.9% to 22.1% of the population (Roth et al., 2011). A recent meta-analysis of these deficits reported that individuals with insomnia appear to be impaired in the domains of episodic memory, problem solving, manipulation in working memory, and retention in working memory, though effect sizes were in the small to moderate range (Fortier-Brochu et al., 2012). However, there is some indication that the cognitive impairment observed in insomnia may be dose-dependent. In an analysis of 16 individuals with primary insomnia and 16 healthy controls, Szelenberger and Niemcewicz (2000) found that the degree of learning impairment on a test of immediate recall correlated with participants' scores on the Athens Insomnia Scale. Moreover, cognitive deficits in this sample appeared to be unrelated to self-reported levels of daytime sleepiness.

There is some evidence that cognitive behavioral therapy for insomnia (CBT-I), a psychotherapeutic intervention that is gaining empirical support for the non-medication treatment of insomnia, may also improve cognitive functioning. In a pilot, randomized controlled trial of CBT-I and sleep hygiene in a sample of individuals with fibromyalgia, a condition frequently associated with disrupted sleep, CBT-I was associated with improvements in alertness, executive functioning, and overall daily functioning (Miró et al., 2011). Similar to OSA, impairments in daytime functioning and work performance are frequent occurrences among individuals with insomnia (Bonnet et al., 2000; Schweitzer et al., 1992; Stepanski et al., 1988). One study of the professional consequences of insomnia found that individuals with insomnia missed work twice as often as good sleepers, had higher rates of accidents while driving, and reported less self-esteem, job satisfaction, and efficiency at work compared to good sleepers (Léger et al., 2006). To date, no studies have examined the efficacy of psychotherapeutic interventions for insomnia on improving work performance; however, there is some evidence that the medication zolpidem is associated with improvements in work performance among individuals with insomnia (Erman et al., 2008).

Cognitive consequences of acute and chronic sleep deprivation

Although the aforementioned data on cognitive and occupational dysfunction in sleep disorders highlights the role disrupted sleep may play in BD, experimentally controlled studies of both acute and chronic sleep deprivation may give a clearer picture of how this mechanism may operate in individuals with BD. Relative to studies of total sleep deprivation, there have been fewer studies conducted on partial sleep deprivation (less than 7 hours of sleep in a 24 hour period) and chronic partial sleep deprivation, the types of sleep deprivation that may be more relevant to what is observed in BD. However, evidence suggests that mood and cognition are more impaired following partial than total sleep deprivation (Durmer & Dinges, 2005), further suggesting that these specific types of sleep restriction be given special attention within the context of BD.

In an extensive review, Durmer and Dinges (2005) reported cognitive slowing, decreased response time, decline in short-term recall and working memory, and reduced learning as a result of experimentally induced sleep deprivation. Sleep deprivation seems to also adversely affect prefrontal cortex-related executive attention and working memory abilities, which is further demonstrated by neurophysiological studies that identify activity in the PFC during sleepiness (Drummond et al., 1999; 2001). In one study, short-term sleep deprivation (24 hours) produced a decrease in global cerebral glucose metabolism as well as relatively reduced cerebral glucose metabolism in the thalamus and PFC (Thomas et al., 2000). Interestingly, a comprehensive review of the neurobiological underpinnings of BD pointed to the thalamus as a key brain structure in the etiology of BD due to its function (Ng, W.X.D et al., 2009), whereas a 2010 examination of thalamic volumes in individuals with BD

demonstrated smaller volumes of the right thalamus in bipolar patients compared to normal controls (Radenbach et al., 2010).

A 2003 study of dose-specific sleep restriction supported earlier claims of neurocognitive deficits following sleep restriction, but also provided evidence that reductions in sleep to just 6 hours of sleep per night may have adverse effects on cognitive performance and daily living (Van Drogen et al., 2003). In that study, 72 hours of total sleep deprivation (the most extensive of the sleep deprivation groups) was associated with more cognitive impairment than any of the partial sleep-deprivation groups (which were limited to 4, 6, or 8 hours in bed). As expected, no cognitive deficits were reported following 8 hours in bed, but after two weeks of chronic sleep restriction to 4 hours per night, performance on measures of attention and memory were comparable to that of the group that endured 72 hours of total sleep deprivation. In a similar fashion, those restricted to 6 hours of sleep per night demonstrated cognitive functioning comparable to one night's total sleep deprivation. It would appear, then, that at about 7 hours of sleep per night or less, there is some evidence of cognitive consequences. This is with the understanding, however, that this is an average number, and there is considerable individual variability in terms of the amount of sleep needed to feel alert and refreshed, as well as age-related decreases in sleep need across the lifespan.

It is important to note that during phases of mania and hypomania in BD, patients often report a decrease in subjective "need" for sleep, with some individuals reporting feeling fine after only 2 to 3 hours of sleep. However, this is not to say that the individual does not objectively need this sleep, and that there are not significant neurocognitive consequences of this sleep deprivation. Indeed, as the above research on healthy individuals suggests, cognitive decline seems to operate as a function of the duration of sleep deprivation, such that performance is poorer with each subsequent day of reduced sleep. Reports on clinical variables associated with cognitive deficits have often identified illness severity and duration of illness as key variables. These clinical predictors may be explained in terms of sleep disturbance if we consider the length of manic episodes as well as the total amount of sleep lost (e.g., a week-long mania where a patient gets about 2 to 3 hours of sleep per night or a month-long hypomania where a patient reports 6 hours of sleep per night). Moreover, as earlier sections of this review attest, there is often limited recovery in the inter-episode period of BD with a great number of patients reporting persistent sleep disturbance despite euthymic mood. With studies of healthy individuals suggesting more than one night of "recovery sleep" may be necessary to return to previous levels of cognitive functioning following chronic sleep restriction (Dinges et al., 1997), one can infer that if individuals with BD do not get adequate sleep recovery, their cognitive functioning will fail to improve sufficiently.

Some neurophysiological correlates of chronic sleep deprivation have been uncovered that may be relevant to the study of BD. In rats, chronic sleep restriction has been shown to cause a decrease in hippocampal volume, which is not explained by changes in glucocorticoid levels or neurogenesis (Novati et al., 2011). The hippocampus has been implicated in the etiology of BD due to activity identified during attentional, memory, and emotional tasks in fMRI studies (Benicio et al., 2007). Recently, sleep deprivation has been shown via fMRI to amplify reactivity in the mesolimbic reward networks in response to pleasure-evoking stimuli (Gujar et al., 2011). This finding is noteworthy in the context of the Behavioral Approach System (BAS) model of the etiology of BD that hypothesizes that individuals with BD have a hypersensitivity to reward, and stimuli relevant to the BAS system (e.g., goals, challenges, achievements, as well as failures and losses) evoke cognitive and affective responses in the corresponding valence (manic or depressive) (Alloy & Abramson 2010). Indeed, recent research suggests a possible behavioral overlap in the

circadian and reward systems, as evidenced by a diurnal rhythm of positive affect in a naturalistic setting, as well as a 24 hour rhythm of positive affect that is synchronous with the circadian rhythm in the absence of environmental variation in reward (Murray et al., 2009).

In terms of the temporal relationship of cognitive deficits, namely executive functioning deficits, and sleep disturbance, there is some evidence suggesting that sleep loss may not necessarily *cause* executive functioning deficits in all cases, but that an underlying executive deficit may make an individual more prone to sleep problems. Killgore et al. (2009) tested the hypothesis that higher baseline executive function may predict resiliency to cognitive deterioration following sleep loss. The authors recruited 54 healthy volunteers and selected the upper and lower quartiles based on performance on a vigilance task in order to gauge resiliency to fatigue. The upper quartile scored higher on a battery of executive tests (Stroop, letter fluency, trail making) but there were no group differences on non-executive tasks. In light of these findings, researchers should examine the possibility that baseline deficits in executive functioning may make an individual more susceptible to the cognitive effects of sleep deprivation.

Tying Together the Evidence: Guidelines for Further Research

Thus far, we have discussed how sleep disturbance has been found to be associated with numerous cognitive impairments including attention, memory, and executive functioning. We have seen from the literature on cognitive functioning in BD that many of these same systems are reported to be impaired, but with no direct analyses examining the role of sleep variables in the etiology of these deficits. We also have reviewed evidence of sustained functional impairment in the euthymic phase of BD as well as evidence of poor work performance among individuals with insomnia and sleep-related breathing disorders. From many standpoints, there is theoretical support for the hypothesis that sleep disturbance may contribute to sustained cognitive deficits in BD.

However, the evidence reviewed thus far must be interpreted through the lens of the inherent complexity of BD. To simply state that sleep disturbance contributes to cognitive deficits would be to gloss over many potentially important processes that may either interact or act in parallel with the mechanism outlined in this review. Additionally, as not all individuals with BD experience sleep disturbance, and as not all experience cognitive deficits, we cannot equivocally claim that this process is universal to the disorder. Thus, it is important to address possible mechanisms of action of the sleep disturbance/cognitive deficit hypothesis, as well as discuss how these possible processes can be examined in future studies.

One possible theory is that there are distinct types of cognitive endophenotypes in BD: one type consisting of endogenous cognitive deficits (see Figure 1 top), the other consisting of primarily sleep-mediated cognitive deficits (see Figure 1 middle), and a third consisting of both endogenous and sleep-mediated cognitive deficits (see Figure 1 bottom). Several reviews have been cited in this review that point toward a cognitive endophenotype for BD, with domains of executive functioning, attention, and verbal memory considered to be potential candidates due to the deficits observed in first degree relatives of individuals with BD. Researchers also have discovered that several genes that are known to play important roles in circadian rhythm regulation are also associated with BD, albeit to a relatively modest degree (Harvey et al., 2008). Thus, it is important to examine the extent to which some individuals with BD may possess an underlying susceptibility to *both* sleep disruption and neurocognitive impairment, and whether these individuals exhibit poorer functional outcome as well as more severe clinical course. As evidenced by the multiple processes with which sleep and cognitive functioning may interact or operate in parallel (Figure 1), the

proposition of a distinct sleep/cognitive functioning mechanism serves to fine-tune existing hypothetical mechanisms rather than replace them with a universal explanation for poor functional outcome.

Toward that end, it may be useful to discuss ways in which data already reported in this review might be examined through the lens of a sleep and cognitive deficit framework. For example, the Bonnin et al (2010) report found that, in addition to the association between neurocognitive variables and poor functional outcome, the only clinical variable associated with functional outcome was residual depressive symptoms as measured by the Hamilton Rating Scale for Depression (HRSD). However, the authors did not explore specifically which symptoms were associated with poor outcome. Four of the 21 items on the HRSD are sleep-related (initial, middle, terminal, and hypersomnia), and it would be informative to examine what proportion of the HRSD scores were comprised of sleep disturbance, and to what extent these symptoms were associated with the reported neurocognitive deficits. In cases such as this Bonnin et al report, as well as the Martinez-Aran reports of conflicting data concerning associations between clinical variables and functional outcomes, examining the contribution of sleep disruption to clinical ratings may help explain some of the disparities. The results of the Gilbert et al. (2010) study of cognitive functioning and employment trajectory also would be more informative if examined with a sleep and cognitive functioning approach. The authors found that mood state was not associated with employment status, but there was no explicit mention of sleep quality, and thus no way to determine if the self-reported difficulties with attention were potentially mediated by sleep disturbance.

The sleep and cognitive functioning framework also serves to pose questions about the mechanism of action of a psychotherapy that has been shown to improve occupational functioning in BD. Frank et al. (2008) found that adjunctive treatment with Interpersonal and Social Rhythm Therapy, a therapy that along with the standard tenets of Interpersonal Psychotherapy for depression includes a social rhythm and sleep stabilization component, was associated with more rapid improvement in occupational functioning compared to medical case management. The authors attribute this result to the therapy's focus on interpersonal and role functioning, but it is theoretically possible that the stabilization of sleep resulted in cognitive improvements, which, by extension, had a positive impact on occupational functioning.

The points made above should not be mistaken for the refutation of the existence of endogenous cognitive deficits in BD that are distinct from those potentially generated or exacerbated by sleep disruption. However, the consideration that there may be separate subsets of individuals who possess sleep-mediated cognitive deficits and/or the combination of sleep-mediated and endogenous cognitive deficits could answer important questions about differential response rates to various treatments (e.g., IPSRT) and inform research into more targeted interventions. Toward that end, we have outlined suggestions for examining this novel approach.

1. Maintain consistency between BD and sleep disorder/sleep deprivation literatures—

One of the obstacles in making comparisons between tests of cognitive functioning in the sleep literature versus the BD literature is the wide variety of tests used to measure various domains of cognitive functioning. Indeed, this is an obstacle mentioned in many meta-analyses of cognitive functioning in BD. Going forward, studies should attempt to utilize cognitive tests that have been tested widely in both samples. Specifically, researchers are invited to design studies that incorporate the Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985), a sustained attention reaction-timed task that measures the speed with which participants respond to a visually presented stimulus. The PVT has been

used in a large number of studies and has been found to be highly sensitive to sleepiness in a number of experimental and clinical contexts (Dorrian et al., 2005). Studies with bipolar samples would be better able to compare neurocognitive measures of attention to reports on non-bipolar samples if this measure were included in the test battery. Additionally, steps should be taken to be consistent with measures of executive functioning, especially in light of conflicting reports of broad dysexecutive syndrome vs. more specific executive impairments in the bipolar literature. As executive functioning can envelop a wide range of cognitive abilities, researchers should do their best to select tests that share the least overlap with other cognitive domains and that have been previously reported in the literature.

2. Include more ecologically valid tests of cognitive functioning—One of the goals of this review was to examine possible contributors to sustained functional impairment in BD. In order to examine whether chronic sleep disturbance contributes to the sustained cognitive impairment discussed in this review, and in order to examine whether impairments in both of these domains are responsible for such persistent disability, it is particularly important that we begin to incorporate more ecologically valid tests in order to determine the degree to which cognitive impairment translates into difficulties with real-world functioning. The O'Shea et al. (2010) study is a good example of a neuropsychological test battery that produces findings that are more easily generalizable to everyday functioning.

Ecological validity and generalizability of findings are important for the development of rehabilitation-focused outcome research. The persistence of functional disability throughout the inter-episode period in BD highlights the need for treatments that are geared toward rehabilitation. If the sleep/cognitive functioning hypothesis is supported empirically, it may behoove researchers to develop new interventions, or expand upon existing interventions, that take advantage of the euthymic period as a key time-point for rehabilitation. Most treatments are developed to care for patients in the throes of an affective episode. The fact that patients are free from mood impairment during the inter-episode period might make sleep and cognitive rehabilitation programs more effective. In a similar vein, treatment outcome studies involving IPSRT may want to incorporate pre- and post-tests of cognitive functioning to determine whether stabilizing sleep would help bring about improvements in the cognitive domains thought to be most vulnerable to sleep disturbance.

3. Repeat studies of sleep architecture to predict to cognitive functioning—If we want to examine the ways in which sleep impacts cognitive functioning, it will not be sufficient to know merely that sleep as a broad system is associated with deficits in cognitive functioning. Studies that examine slow wave sleep, REM sleep, Stage 2 sleep, etc. will help elucidate what aspects of sleep disturbance may or may not be related to neurocognitive performance. Detailed polysomnography studies using healthy control groups as well as experimentally controlled sleep-deprived comparison groups may further pinpoint what aspects of sleep may play a role in either the development or maintenance of cognitive deficits.

4. Examine the role of psychological components and vulnerabilities—If sleep disruption and cognitive functioning are indeed related, there are psychological components that may be relevant to this underlying mechanism. For example, it was previously noted that subjective reports of disturbed sleep were often present when objective data were non-significant. Indeed, Harvey et al. (2005) noted greater levels of dysfunctional attitudes towards sleep among BD patients relative to controls. In a similar vein, researchers may want to consider the idea that a bipolar episode can serve as a life event in and of itself, thus perpetuating the insomnia. As is the case with BD, stressful life events have been shown to precipitate insomnia (Bastein et al., 2004; Healy et al., 1981; Morin et al., 2003). Thus, lines of research examining cognitive vulnerability to sleep disruption may be worth pursuing in

bipolar samples. Moreover, this psychological component suggests that portions of cognitive-behavioral therapy for insomnia (CBT-I) may be indicated for BD patients. Sleep restriction therapy, one of the core behavioral components of CBT-I, is often contraindicated for BD patients due to the elevated risk of mania following decreased sleep. However, as psychotherapeutic interventions for BD continue to develop, including the cognitive strategies in CBT-I may be beneficial to those with inter-episode sleep disturbance.

Conclusion

This review attempted to draw together three separate lines of research that, to date, have not been examined from a unified perspective: evidence of sustained sleep disruption throughout the inter-episode or euthymic phase of BD, evidence of sustained neurocognitive deficits throughout the inter-episode phase, and evidence of neurocognitive deficits in sleep disorders as well as marked neurocognitive consequences of both acute and chronic sleep deprivation in healthy individuals. When these separate lines of research are integrated, the groundwork is laid for a theoretical model of BD that incorporates sleep disruption as being either a predisposing factor or exacerbator of neurocognitive deficits throughout the illness course, resulting in sustained functional impairment despite the remission of mood symptoms. Future research should examine the degree to which sleep disruption may contribute to the presence and magnitude of neurocognitive deficits, whether sleep disruption and neurocognitive functioning interact to maintain functional impairment, and whether a unique sleep and neurocognitive-specific endophenotype of BD may exist.

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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

Figure 1. Possible roles of sleep and cognitive functioning in producing poor functional outcomes in inter-episode BD

* e.g., increased risk taking/poor judgment, social withdrawal, increased arguments/ impaired relationships

Table 1**Studies of Sleep Disruption in Euthymic Bipolar Patients**

Study	N (BD)	% of sample with sleep disturbance	Type of sleep disturbance	Methodology
Sylvia et al., 2011	483	15% (n = 73)	Reduced sleep (item 4 on MADRS)	Clinical Interview
Millar et al., 2004	19	100%	Longer sleep duration, onset latency, greater variability in sleep in bipolar group	Actigraphy, self-report
Jones et al., 2005	19	n/a; no significant differences in sleep vs. controls	No significant sleep disturbance	Actigraphy
Sitaram et al., 1982	14	N/A	Participants with BD have higher density of eye movements during first REM; earlier onset of second REM period in remitted BD	Polysomnography
Brill et al., 2011	106	23.6% (n = 25)	Delayed sleep onset; middle insomnia	Retrospective chart review
Giglio et al., 2009	190	58.42% (n=111)	Initial, middle, and terminal insomnia	Clinical Interview
Harvey et al., 2005	20	70%	Initial and middle insomnia	Actigraphy, self-report