Title

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Publication Date

2015

Peer reviewed|Thesis/dissertation

The Association between Insomnia-related Sleep Disruptions and Cognitive Dysfunction during the Inter-episode Phase of Bipolar Disorder

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A dissertation submitted in partial satisfaction of the

requirements for the degree of

doctor of Philosophy

in

Psychology

in the

Graduate Division

of the

University of the California, Berkeley

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Summer 2016

Abstract

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Sleep disturbance and cognitive dysfunction are two key domains of impairment during the inter-episode phase of bipolar disorder. Despite considerable evidence demonstrating the importance of sleep for cognition in healthy and sleep-disordered samples, this link has been minimally examined in bipolar disorder. Thus, the present study tested the association between insomnia-related sleep disruptions and cognitive functioning during inter-episode bipolar disorder. Forty-seven participants with bipolar disorder and a comorbid insomnia diagnosis (BD-INSOMNIA) and 19 participants with bipolar disorder without sleep disturbance in the last six months (BD-CONTROL) participated in the study. Two domains of cognitive functioning were assessed: working memory and verbal learning. Insomnia-related sleep disruptions were assessed both categorically (i.e., insomnia diagnosis) and dimensionally (i.e., total wake time, sleep duration, and sleep duration variability). Hierarchical linear regressions, adjusting for participant age, demonstrated that insomnia diagnosis did not have an independent or interactive effect on cognition. However, regardless of insomnia diagnosis, greater total wake time predicted poorer working memory performance and greater sleep duration variability predicted poorer working memory and verbal learning performance. Further, following sleep treatment, a reduction in total wake time predicted improved working memory performance and a reduction in sleep duration variability predicted improved verbal learning performance. These findings raise the possibility that sleep disturbance may be one mechanism underlying cognitive dysfunction in bipolar disorder and highlight the importance of treating sleep disturbance in bipolar disorder.

The Association between Insomnia-related Sleep Disruptions and Cognitive Dysfunction during the Inter-episode Phase of Bipolar Disorder

Bipolar disorder is one of the 10 most disabling conditions worldwide (World Health Organization, 2001) and has a lifetime prevalence ranging from 0.4 – 2.4% (e.g., Merikangas et al., 2011). It was originally conceptualized as a disorder of mood episodes and periods of complete symptom remission between episodes (American Psychiatric Association, 1952). However, it is now known that a large percentage of individuals with bipolar disorder continue to experience substantial impairment during periods identified as neither depressive nor manic, a phase referred to as the *inter-episode period* (Judd et al., 2003; MacQueen et al., 2003; Robb, Cooke, Devins, Young, & Joffe, 1997). Sleep disturbance and cognitive dysfunction are two important domains of impairment during the inter-episode period, each contributing to functional impairment and reduced quality of life (e.g., Harvey, Schmidt, Scarna, Neitzert Semler, & Goodwin, 2005; Robinson et al., 2006). Yet, despite substantial literature demonstrating a link between sleep and cognition in healthy and sleep-disordered samples, the association between sleep disturbance and cognitive dysfunction during inter-episode periods of bipolar disorder has been minimally examined.

Sleep disturbance is a core feature of the inter-episode period of bipolar disorder, with seventy percent of individuals reporting clinically significant sleep problems during these inter-episode states (Harvey et al., 2005). These sleep difficulties include hypersomnia (Kaplan, Gruber, Eidelman, Talbot, & Harvey, 2011; Kaplan et al., 2015; Ritter et al., 2012), delayed sleep phase (Giglio et al., 2012), irregular sleep patterns (Eidelman, Talbot, Gruber, & Harvey, 2010; Jones, Hare, & Evershed, 2005; Millar, Espie, & Scott, 2004), and most commonly, insomnia (Harvey et al., 2005; Millar et al., 2004; Rocha, Neves, & Correa, 2013). Over half (55%) of individuals with bipolar disorder meet diagnostic criteria for insomnia during the inter-episode phase (Harvey et al., 2005). Insomnia is defined by subjective difficulty falling asleep, staying asleep, or waking up too early, despite adequate opportunity to sleep, with associated daytime impairment or distress (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2013). Note that insomnia is not only characterized by difficulties with sleep initiation and/or maintenance but is also associated with short sleep duration (Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009a; Vgontzas et al., 2009b; Vgontzas et al., 2010) and night-to-night variability in sleep behaviors (e.g., bedtime, rise time, sleep duration; Buysse et al., 2010; Frankel, Courset, Buchbinder, & Snyder, 1976). Interestingly, fragmented sleep, shortened sleep duration, and elevated variability in sleep behaviors are also observed during inter-episode bipolar disorder, regardless of insomnia diagnosis (Eidelman et al., 2010; Geoffroy et al., 2014; Gruber et al., 2009; Jones et al., 2005; Kanady, Soehner, & Harvey, 2015; Millar et al., 2004; Ritter et al., 2012).

Cognitive dysfunction is another prominent feature of the inter-episode period of bipolar disorder. The cognitive deficits commonly documented during the inter-episode phase span a range of domains, including executive functioning and verbal learning (Adler, Holland, Schmithorst, Tuchfarber, & Strakowski, 2004; Ferrier, Stanton, Kelly, & scott, 1999; Frangou, 2005; Haldane et al., 2008; Russo et al., 2015; Zubieta, Huguelet, O'Neil, & Giordani, 2001). Executive functioning is an umbrella term comprising many different cognitive processes, such as planning, working memory, attention, problem solving, inhibition, mental flexibility, and task switching. Although many of these processes are impaired during the inter-episode period, some of the largest effect sizes have been found for performance on tasks of working memory

(Robinson et al., 2006). Working memory is a system for temporarily storing and managing information so that it is easily accessible and can be utilized to carry out a task (Baddeley, 1992). In addition to deficits in working memory, verbal learning is also impaired during the inter-episode period (Cavanagh, Van Beck, Muir, & Blackwood, 2002; Russo et al., 2015). In one study, an inter-episode bipolar disorder group performed significantly worse *only* on a task of verbal learning (Cavanagh et al., 2002). This finding is consistent with meta-analyses demonstrating medium to large effect sizes for deficits on tasks of verbal learning and memory during the inter-episode phase (Arts, Jabben, Krabbendam, & van Os, 2008; Robinson et al., 2006).

As is evident, it is well established that both sleep disturbance and cognitive dysfunction are prevalent features of the inter-episode phase of bipolar disorder. However, the potential contribution of sleep disturbance to inter-individual variation in cognitive dysfunction is under-characterized, despite the evidence demonstrating the association between sleep and cognition in healthy and insomnia samples (see Boland & Alloy, 2013 for a review). Previous studies using sleep deprivation paradigms have unequivocally demonstrated the importance of sleep for cognition in healthy individuals. These studies have demonstrated that sleep deprivation prior to learning is associated with a 40% reduction in the ability to learn new material (Yoo, Hu, Gujar, Jolesz, & Walker, 2007) and impairs performance across a variety of tasks including working memory (e.g., Alhola & Polo-Kantola, 2007; Chee & Choo, 2004; Lim & Dinges, 2010) and verbal learning and memory (e.g., Drummond et al., 2000).

The association between insomnia and cognition has been studied extensively, but with varied findings. Adults diagnosed with insomnia consistently report subjective cognitive deficits (e.g., Orff, Drummond, Nowakowski, & Perlis, 2007; Roth & Ancoli-Israel, 1999; Varkevisser, Van Dongen, Van Amserdam, & Kerkhof, 2007). However, when comparing objective cognitive performance across persons with insomnia and healthy sleepers, the evidence is mixed. Some studies report that insomnia is associated with objective cognitive impairment (Edinger, Means, Carney, & Krystal, 2008; Schneider, Fulda, & Schulz, 2004; Varkevisser & Kerkhof, 2005) but other studies reveal no such relation (Orff et al., 2007; Varkevisser et al., 2007). One explanation for these mixed findings is that there may be specific sleep disruptions related to insomnia that drive the association with cognition. For example, research examining insomnia-related sleep disruptions and cognition in older adults have found that more time spent awake in the middle of the night (Blackwell et al., 2006; Blackwell et al., 2014; Naismith et al., 2010; Wilckens, Hall, Nebes, Monk, & Buysse 2015) and longer sleep latency (Blackwell et al., 2006; Luik et al., 2015) are associated with greater cognitive deficits. Insomnia coupled with short sleep duration (<6 hours) also appears to have a greater impact on cognitive dysfunction when compared to insomnia with normal sleep duration and healthy sleep patterns (Fernandez-Mendoza et al., 2010). Although variability in sleep behaviors is a core aspect of insomnia, only one study has examined the impact of sleep variability on cognition (McCrae, Vatthauer, Dzierzewski, & Marsiske, 2012), revealing that night-to-night variability in sleep duration and total wake time did not predict performance on a processing speed or an executive functioning task in a sample of older adults. As night-to-night variability in sleep behaviors is a common feature of insomnia, more research is needed to further parse out this association.

Only recently has the association between sleep and cognition during inter-episode bipolar disorder been examined with three studies starting the process of better understanding this connection. The first found that individuals with bipolar disorder who demonstrate poorer cognitive performance on a neuropsychological battery report higher rates of insomnia compared

to individuals with bipolar disorder who demonstrate intact cognitive performance (Volkert et al., 2015). However, sleep disturbance was assessed using items from a depression rating scale. Using post-hoc exploratory correlational analyses, the second demonstrated a relation between Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) rated daytime dysfunction and a working memory task (Boland et al., 2015). The third demonstrated that poorer performance on measures of working memory, visual learning, and social cognition was associated with patient ratings of poor sleep quality and increased daytime sleepiness (Russo et al., 2015).

The overall objective of the present study was to build upon these findings by further clarifying the association between sleep and cognition during inter-episode bipolar disorder. The first aim was to examine whether insomnia diagnosis and insomnia-related sleep disruptions – in particular total wake time, sleep duration, and sleep duration variability – have an independent or interactive effect on working memory and verbal learning performance during the inter-episode phase. These particular disruptions were selected because they represent core features of insomnia (e.g., American Psychiatric Association, 2013; Buysse et al., 2010; Vgontzas et al., 2009a), they are common during the inter-episode phase (Eidelman et al., 2010; Gruber et al., 2009; Jones et al., 2005; Millar et al., 2004), and they have been associated with objective cognitive performance in healthy and insomnia samples with the exception of sleep duration variability (e.g., Blackwell et al., 2014; Naismith et al., 2010; Wilckens et al. 2015; Yoo et al., 2007). Although sleep duration variability has not yet been shown to be associated with cognition, we selected this variable because (a) sleep duration is strongly related to cognition (e.g., Yoo et al., 2007), (b) sleep duration variability is an ecologically valid and accurate approach to measuring sleep duration across the week (e.g., McCrae et al., 2012), (c) night-to-night variability in sleep duration is highly prevalent during the inter-episode period (e.g., Ng et al., 2015), and (d) variability of sleep duration and cognitive dysfunction are both associated with quality of life in bipolar disorder (Lemola et al., 2015; Brissos, Dias, & Kapczinski, 2008). Tasks of working memory and verbal learning were selected because previous research suggests that these domains are the most impaired during the inter-episode period of bipolar disorder (e.g., Robinson et al., 2006; Russo et al., 2015). In addition, these domains are impaired in individuals with insomnia (e.g., Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2011) and following sleep deprivation (e.g., Drummond et al., 2000; Lim & Dinges, 2010). Based on the mixed findings of previous research, we tested two competing hypotheses: (1) there would be a main effect of insomnia diagnosis and an interactive effect whereby insomnia diagnosis *and* greater total wake time, shorter sleep duration, or greater sleep duration variability in the insomnia group would predict poorer cognitive performance, versus (2) greater total wake time, shorter sleep duration, and greater sleep duration variability would independently predict poorer cognitive performance, regardless of insomnia diagnosis.

The second aim was to determine if working memory and verbal learning performance improves following a form of cognitive behavior therapy for insomnia modified specifically for bipolar disorder (CBTI-BD; Harvey et al., 2015). We hypothesized that people with bipolar disorder who demonstrated an improvement in the sleep parameters shown to be associated with cognition per the first aim (i.e., total wake time, sleep duration and sleep duration variability) following CBTI-BD would show a related improvement in cognitive performance relative to a control psychoeducation treatment condition.

METHODS

Participants

Forty-seven adults with bipolar disorder and a comorbid insomnia diagnosis (BD-INSOMNIA) and 19 adults with bipolar disorder without sleep disturbance in the last six months (BD-CONTROL) participated in the study. All participants met DSM-IV-TR criteria (American Psychiatric Association, 2000) for bipolar disorder, type I. Participants were inter-episode (i.e., not currently manic or depressed) at the time of the assessment. Inter-episode status was defined by a score of 24 or less on the Inventory of Depressive Symptomatology, Clinician Rating (IDS-C; Rush et al., 1996), a score of 12 or less on the Young Mania Rating Scale (YMRS; Young et al., 1978), and not meeting DSM-IV-TR criteria for depression, mania, or hypomania in the month preceding the clinical interview. All participants were at least 18 years old and reported English fluency, which was necessary as all aspects of the protocol were in English. Given the standards of care for the treatment of bipolar disorder and to enhance the generalizability of the results, we did not exclude participants based on medication use. However, participants were required to be on a stable medication regimen (i.e., no changes in the dosage or frequency of medication use) for at least four weeks prior to enrollment in the study as side effects are more likely early in treatment than with continued use (Ketter & Wang, 2002).

Exclusion criteria for both groups included the following: an alcohol and/or substance use diagnosis within the past three months based on DSM-IV-TR criteria (American Psychiatric Association, 2000); a current post-traumatic stress disorder diagnosis based on DSM-IV-TR criteria (American Psychiatric Association, 2000); an active or progressive neurodegenerative disease or physical illness; evidence of sleep apnea, restless legs syndrome, or periodic limb movements during sleep preliminarily assessed by the Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2009) and the Berlin sleep apnea questionnaire (Sharma et al., 2005) and if necessary, confirmed with overnight polysomnography; employment as an overnight shift worker in the last three months; current suicidal risk, specifically endorsements of active suicidal intent and/or a specific suicide plan; attempted suicide within the past 6 months; current homicidal risk (as assessed by treating physician); and pregnancy and/or breast-feeding mothers.

Participants in the BD-INSOMNIA group also met criteria for current insomnia. Insomnia was defined as a subjective report of difficulty falling asleep (>30 minutes), difficulty maintaining sleep (wake after sleep onset >30 minutes), and/or waking up too early (early morning awakening >30 minutes), with associated daytime complaints, at least three times a week for at least one month as verified by the Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2009) and a daily sleep diary. Further, these sleep difficulties had to occur despite adequate opportunity to sleep. These criteria reflect a combination of criteria from the Research Diagnostic Criteria (RDC; Edinger et al., 2004), International Classification of Sleep Disorders (ICSD-2; American Academy of Sleep Medicine, 2005), and DSM-5 standards (American Psychiatric Association, 2013). Notably, the inter-episode period of bipolar disorder is associated with several different types of sleep disturbance, such as circadian disruption (e.g., Giglio et al., 2010) and hypersomnia (e.g., Kaplan & Harvey, 2008) and these different types of sleep disturbance often co-occur (e.g., Kanady et al., 2015). Moreover, prescription sleep medication (e.g., Zolpidem) is often the first line of treatment for insomnia in bipolar disorder (e.g., Shaffer, Schaffer, Millaer, Hang, & Nordahl, 2011; Satter, Ramaswamy, Bhatia, & Petty, 2003). Therefore, to enhance generalizability, we did not exclude for the presence of other sleep

disorders with the exception of obstructive sleep apnea, restless leg syndrome, and periodic leg movements nor did we exclude for sleep medication and/or sleep aid use.

Participants in the BD-CONTROL group were excluded if they endorsed a clinically significant sleep disorder (e.g., insomnia, hypersomnia, delayed sleep phase, sleep apnea, restless leg syndrome, periodic leg movement, etc.) in the last six months as assessed by the DSISD (Edinger et al., 2009) and/or if they reported difficulty falling asleep (>30 minutes), difficulty maintaining sleep (wake after sleep onset >30 minutes), and/or waking up too early (early morning awakening >30 minutes) at least three times a week on the daily sleep diary. Sleep medications and sleep aids, including hypnotic use (e.g., Ambien), off-label prescriptions (e.g., mood stabilizers prescribed to treat sleep), over-the-counter sleep aids, and alcohol and/or marijuana use with the intention of promoting sleep, were also exclusionary.

Procedure

All procedures described were approved by the Committee for Protection of Human Subjects at the University of California, Berkeley. Participants in the BD-INSOMNIA group were recruited as part of a larger NIMH-funded treatment study (R34MH080958). Participants in the BD-CONTROL group were recruited separately. All participants were recruited through Internet advertisements and flyers distributed to psychiatric clinics in the community.

All participants first completed a phone screen to establish preliminary eligibility. Participants were then invited for a detailed in-person pre-treatment clinical assessment. Prior to the pre-treatment clinical assessment, participants were sent sleep diaries and instructed to complete the sleep diary every morning for the week prior to the assessment. During the pre-treatment clinical assessment, written informed consent was obtained, demographic data were recorded, and self-report measures including the Insomnia Severity Index (ISI; Morin, 1993; Morin et al., 2011) and Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) were completed. Information about medication use was collected using a Pharmacotherapy Tracking Log (Harvey et al., 2015). Bipolar diagnoses were confirmed using the Structured Clinical Interview for Axis I Disorders (SCID; First et al., 1995). The IDS-C and YMRS, in addition to the information obtained during the SCID, were used to establish a current inter-episode state. In the BD-INSOMNIA group, the DSISD (Edinger et al., 2009) and sleep diaries were used to establish insomnia diagnoses. In the BD-CONTROL group, the DSISD and sleep diaries were used to screen for the presence of a sleep disorder in the last six months. Approximately one week after the pre-treatment clinical assessment, participants in the BD-INSOMNIA group returned to the lab for their pre-treatment cognitive assessment. Participants in the BD-CONTROL group were given a lunch break after the clinical assessment and were asked to return to the lab that afternoon for their cognitive assessment. The rationale for completing the pre-treatment clinical assessment and pre-treatment cognitive assessment during the same day for the BD-CONTROL group was to reduce participant burden, as these participants were not returning to the lab for sleep treatment. During the pre-treatment cognitive assessment, participants completed a battery of neuropsychological tests, including the N-back, digit span, and verbal learning tasks as a part of a larger protocol. Cognitive assessments were always initiated between 3:00 PM and 4:00 PM in order to control for circadian differences that have been shown to influence cognition (e.g., Dijk et al., 1992).

Only participants in the BD-INSOMNIA group received sleep treatment. Participants in the BD-INSOMNIA group were randomized to one of two treatment conditions: CBTI-BD or Psychoeducation (Harvey et al., 2015). Following eight weekly sessions of treatment, the BD-

INSOMNIA group returned to the lab for a post-treatment assessment. Post-treatment assessment procedures were identical to the pre-treatment clinical and cognitive assessments. In order to eliminate possible confounding variables (e.g., fatigue, exposure to tasks, circadian effects, etc.), all measures were completed in the same order as the pre-treatment assessment, different versions of the cognitive tasks were administered, and the post-treatment assessment was also conducted between 3:00 PM and 4:00 PM. Given the level of difficulty of the working memory and verbal learning tasks, all participants practiced different versions of these tasks prior to each cognitive assessment. Participants in the BD-INSOMNIA group completed sleep diaries for the duration of the study.

Measures

Clinical Measures

The Structured Clinical Interview for DSM-IV (SCID; First et al., 1995) was administered to assess for DSM-IV-TR Axis I disorders and to determine DSM-IV-TR bipolar episodes (mania, hypomania, depression). The SCID has good reliability (Skre et al., 1991; Williams et al., 1992). Randomly selected audiotapes of SCID interviews (15%) were rated by a set of independent reviewers in order to check diagnostic reliability. Ratings matched 100% ($\kappa = 1.00$) of the primary diagnoses made by the original interviewer. Although this high level of agreement indicates strong inter-rater reliability, the use of a "skip-out" strategy (implemented if initial required criteria for a particular disorder were not met) may have reduced the number of potential disagreements with the original interviewer.

Young Mania Rating Scale (YMRS; Young et al., 1978). The YMRS is an 11-item measure used to assess the severity of manic symptoms. Specifically, the YMRS was developed to assess the severity of (a) elevated mood, (b) increased motor activity, (c) increased sexual interest, (d) decreased need for sleep, (e) increased irritability, (f) increased speech, (g) increased distractibility, (h) increased goal-directed behavior, (i) disruptive and/or aggressive behavior, (j) appearance, and (k) insight. Each item is rated on a five-point scale and a higher YMRS score indicates more severe manic symptoms. The YMRS is a sensitive measure, and has been shown to have good reliability and validity (Young et al., 1978).

Inventory of Depressive Symptomatology, Clinician Rating (IDS-C; Rush et al., 1996). The IDS-C is a widely used 30-item instrument for assessment of depressive symptoms. The IDS-C includes all nine symptoms for major depressive disorder based on the DSM-IV-TR, including affective, behavioral, cognitive and motivational symptoms. The IDS-C also includes assessment of melancholic and atypical features of major depressive disorder (e.g., hypersomnia) and commonly associated symptoms such as anxious and irritable mood. Each item is rated on a four-point scale and a higher IDS-C score indicates more severe depressive symptoms. The IDS-C has demonstrated good reliability and validity (Rush et al., 1996). Given that we recruited an insomnia sample, sleep items were removed from the IDS-C before calculating the total score for each participant.

Pharmacotherapy Tracking Log (Harvey et al., 2015). Medication use was collected during the pre-treatment clinical assessment using the Pharmacotherapy Tracking Log. For each medication, information about dose, time of day taken, frequency of use, missed doses, and side effects was assessed. This log was sent the prescribing physician to verify.

Sleep Measures

Insomnia Severity Index (ISI). The ISI is a seven-item scale used to evaluate the severity of insomnia (Morin, 1993; Morin et al., 2011). The ISI has demonstrated good reliability, validity, and has strong psychometric properties (Bastien et al., 2001). The seven items of the ISI specifically assess the severity of sleep onset and sleep maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by sleep problems. Each item is rated on a five-point scale. A higher score indicates more severe insomnia.

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a well-validated instrument for characterizing sleep disturbance in clinical samples (Buysse et al., 1998). Respondents are asked to answer questions about their sleep over the last month. The items are divided into seven subscales, which afford measurement of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction. A global sleep quality score is obtained by summing the seven component subscales (total score ranging from 0-21). A global sleep quality score of greater than or equal to five is considered indicative of clinically significant sleep disturbance (Buysse et al., 1989).

Duke Structured Interview for Sleep Disorder (DSISD). The DSISD is a semi-structured interview used to assess DSM-IV-TR (American Psychiatric Association, 2001), ICSD-2 (American Academy of Sleep Medicine, 2005), and research diagnostic criteria for sleep disorders (Edinger et al., 2009). The DSISD has good reliability and validity (Edinger et al., 2009). Trained psychology doctoral students administered the DSISD to all participants to confirm insomnia diagnoses for the BD-INSOMNIA group and to assess for the presence of all sleep disorders in both groups. Fifteen randomly selected audiotapes of DSISD interviews were rated by a set of independent reviewers for diagnostic reliability. Ratings matched 99.4% (κ = 0.99) of the primary diagnoses made by the original interviewer, indicating strong inter-rater reliability. Insomnia diagnosis, as assessed by the DSISD, was used to establish group status (BD-INSOMNIA or BD-CONTROL), which was used as one of the independent variables for the first aim.

Sleep Diary. Sleep diaries are a gold-standard daily self-report measure of sleep (Buysse et al., 2006). Participants record specific aspects of their sleep cycles such as bedtime, rise time, sleep onset latency, duration and number of nocturnal awakenings, and early morning awakenings (Carney et al., 2012). Participants were asked to complete the sleep diary immediately upon awakening and to answer questions pertaining to the previous night of sleep. For the purpose of this study, seven days of sleep diary data prior to the pre-treatment assessment and post-treatment assessment were examined. The sleep variables of interest were total wake time, average sleep duration, and sleep duration variability. **Total wake time** was calculated by adding sleep onset latency (SOL; the amount of time it took each participant to fall asleep), wake after sleep onset (WASO; the number of minutes spent awake in bed after initial sleep onset), and early morning awakenings (EMA; minutes spent awake in the morning before getting out of bed that day) for each night and then averaging across the seven days. **Sleep duration** for each night was calculated by subtracting SOL, WASO, and EMA from total time in bed and then averaging across the week. **Sleep duration variability** was calculated by determining the within subject standard deviation of sleep duration for the week (e.g., Eidelman et al., 2009). Average total wake time, sleep duration, and sleep duration variability served as the remaining independent variables for the first aim. Change in total wake time, sleep duration, and sleep

duration variability from pre-to-post treatment were used to test changes in sleep following CBTI-BD or PE, and constituted three of the independent variables for the second aim.

Neuropsychological Tests

Working Memory: The N-Back Task and Digit Span Task. The N-back and digit span are standard tasks for the assessment of working memory in bipolar disorder (Frydecka et al., 2014; Glahn et al., 2006; Thermenos et al., 2009). The N-Back tests the effect of working memory load on performance (Cohen et al., 1997; Owen et al., 2005). During the N-back, participants are presented with a sequence of letters and the participant is required to provide a motor response whenever a specific letter repeats itself *n*-steps earlier in the sequence. The N-Back was administered via computer and consists of four conditions: 0-back, 1-back, 2-back, and 3-back. Participants completed three blocks for each condition (0-back to 3-back), totaling 12 blocks, and the blocks were presented in a random order. Accuracy scores were computed for each N-back condition. Accuracy scores were calculated by subtracting the total number of correct hits by the total number of false positives.

The digit span task is derived from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Pearson, 2008) and is used to assess the load capacity of working memory. In this task, participants are required to repeat a dictated series of digits forwards (forward digit span) and a different series of digits backwards (backward digit span). Both forward and backward digit span begin with two digits and keep increasing in length and difficulty. The number of correct sequences for forward and backward digit span was the outcome variable for this task.

Performance on the N-back and digit span was condensed into a single working memory composite score based on prior work (e.g., Neuchterlein et al., 2008). The working memory composite score was calculated as follows: First, z-scores were calculated for 0-back, 1-back, 2-back, and 3-back N-back accuracy scores. Then, z-scores were calculated for forward digit span and backward digit span. These 6 z-scores were then averaged to create the working memory composite, which served as a cognitive outcome measure for the first aim. Change in pre-treatment to post-treatment working memory composite scores was a cognitive outcome measure for the second aim.

Verbal Learning: The Verbal Learning Task. Verbal learning tasks that require participants to learn a set of words and recall the words after a short delay are standard for assessing verbal learning and memory in bipolar disorder (Alder et al., 2004; Cavanagh et al., 2002; Martinez-Aran et al., 2004). The verbal learning task used in the present study was administered via computer and has been shown to be sensitive to the effects of sleep loss (Drummond et al., 2000). This task alternates between four experimental and five baseline blocks, starting and ending with a baseline block. Six unrelated words are presented during each block. Participants are told not to memorize the baseline words, but to determine whether they were in all upper case or all lower-case letters. Participants are instructed to actively memorize the experimental words for later testing. A total of 24 experimental words are presented. Immediately following word presentation, participants were asked to write down as many words that they could remember from the experimental blocks (immediate recall condition). Approximately 30 minutes later, they were asked to do the same thing (delayed recall condition). D-prime (d') scores were calculated by subtracting the z-score for number of false positives from the z-score of number of correct hits for both the immediate recall and delayed recall conditions. D' scores for immediate recall and delayed recall were then averaged to create a verbal learning composite score (e.g., Neuchterlein et al., 2008), which served as the second cognitive outcome

measure for the first aim. Change in pre-treatment to post-treatment verbal learning composite scores was a cognitive outcome measure for the second aim.

Treatment Conditions

Cognitive Behavior Therapy for Insomnia for Bipolar Disorder (CBTI-BD). CBTI-BD is a treatment specifically designed to address insomnia in bipolar disorder (Harvey et al., 2015). CBTI-BD is a multi-component, case formulation driven approach. Participants randomized to CBTI-BD treatment practiced evidence-based behavioral, cognitive, and daytime interventions, depending on their case formulation. Behavioral interventions included stimulus control, sleep restriction, regularizing sleep and wake times, sleep hygiene education, and devising a relaxing 'wind-down' routine and a stimulating 'rise up' routine. Cognitive interventions included altering unhelpful beliefs about sleep and reducing sleep-related anxiety, bedtime worry, rumination, and vigilance. Finally, daytime interventions included devising a list of energy-generating activities and incorporating these activities into daily routines. Elements from interpersonal and social rhythm therapy (IPSRT; Frank, 2005), Chronotherapy, and Motivational Interviewing were also incorporated into CBTI-BD treatment (please see Harvey et al., 2015 for additional information).

Psychoeducation (PE). The overarching principle of PE was to provide information, but not facilitate or plan for change. The PE sessions focused on bipolar disorder and mood, mania and depression, prodromes, medications, substance use and diet, exercise and relaxation, self-esteem and sleep in a social context. There was no explicit focus on sleep except for including sleep disturbance as a symptom of bipolar disorder, identifying sleep disturbance as a prodrome of mood episodes, and discussing sleep in a social context. PE controlled for location, experience and skill level of the therapists, number and quality of handouts, therapist attention, amount and frequency of therapist contact, duration of treatment, and the beliefs and expectations about the efficacy of treatment held by patients (please see Harvey et al., 2015 for additional information).

Analysis Plan

Preliminary Data Analysis

Previous research has demonstrated that age, years of education, current manic and depressive symptoms, bipolar illness duration, number of mood episodes, and medication use are associated with cognition in bipolar disorder (for a review, see Robinson et al., 2006). Rather than adjusting for all of these variables and reducing power, preliminary bivariate correlations and independent samples t-tests were used to examine associations between the cognitive outcome variables and baseline sociodemographic and clinical features. All continuous variables with a correlation coefficient of greater than 0.30 and all categorical variables (i.e., medication use) with an effect size of greater than 0.30 were included as covariates in subsequent analyses (e.g., Pocock et al., 2002).

Next, in order to assess the degree of multicollinearity between the independent variables, bivariate correlational analyses were conducted and variance inflation factors were examined to ensure that effects of each sleep variable – total wake time, sleep duration, and sleep duration variability – on cognition were independent. If the correlation coefficient was greater than 0.75 (Tsui et al., 1995) and/or the variance inflation factor was greater than 5 (Craney & Surles, 2002), the variables were considered for exclusion.

Finally, independent sample t-tests and chi-squared tests were conducted to assess baseline differences in demographic and clinical features across the BD-INSOMNIA and BD-CONTROL groups.

Primary Data Analyses

Hierarchical linear regressions were used to examine the two aims of the study. All models were tested to ensure that they met the assumptions of a linear regression. All continuous independent variables were mean centered.

First Aim: Do insomnia diagnosis and insomnia-related sleep disruptions have an independent or interactive effect on cognition? To examine the first aim – whether insomnia diagnosis and insomnia-related sleep disruptions have an independent or interactive effect on working memory and verbal learning performance – two hierarchical regressions were performed with the pre-treatment working memory and verbal learning composite scores as the dependent variables. Interaction terms were calculated by multiplying group (BD-INSOMNIA vs. BD-CONTROL) by continuous insomnia variables (total wake time, sleep duration, and sleep duration variability). Using a stepwise approach, we introduced the covariates determined by preliminary analyses in the first model, group status (1 = BD-INSOMNIA and 0 = BD-CONTROL) in the second model, continuous insomnia-related sleep variables in the third model, and interaction terms in the fourth model.

Second Aim: Does cognition improve as sleep improves following CBTI-BD? Only participants in the BD-INSOMNIA group that completed the post-treatment assessment were included in the analyses for the second aim (N=43). First, we calculated change scores for the sleep parameters of interest. Total wake time and sleep duration variability change scores were calculated by subtracting the participants' post-treatment averages from the participants' pre-treatment averages. The sleep duration change score was calculated by subtracting pre-treatment average from post-treatment average. Calculations were performed in this manner so that all positive change scores indicated an improvement in sleep. To examine changes in cognition, change scores were again calculated by subtracting the pre-treatment composite scores from the post-treatment composite scores. Thus positive change scores indicated an improvement in cognition. Next, interaction terms were calculated by multiplying treatment group (CBTI-BD vs. PE) by continuous insomnia variables (total wake time change score, sleep duration change score, and sleep duration variability change score). Finally, two hierarchical regressions were performed with change in working memory and change in verbal learning as the dependent variables and treatment group (CBTI-BD or PE), change in total wake time, sleep duration, and sleep duration variability as the independent variables. For each hierarchical linear regression, covariates determined by preliminary analyses were introduced in the first model, treatment group (1 = CBTI-BD and 0 = PE) was introduced in the second model, change score for each sleep variable was introduced in the third model, and interaction terms were introduced in the fourth model.

RESULTS

Preliminary Data Analyses

Results of bivariate correlations and independent sample t-tests were used to examine the association between cognitive outcome measures and baseline variables. Years of education, illness duration, number of mood episodes, current depressive symptoms, and current manic symptoms did not meet the $R > 0.30$ cutoff and therefore were not considered as covariates, but

the correlation coefficient for age was greater than 0.30 and thus included as a covariate for subsequent analyses. Independent sample t-tests indicated no differences in cognition based on medication use with the exception of mood stabilizers. Use of a mood stabilizer was associated with better verbal learning performance. Because, however, the effect size was less than 0.30, medication use was not included as a covariate.

Regarding multicollinearity analyses, none of the correlation coefficients among the sleep variables was greater than the 0.75 cut-off (total wake time and sleep duration: r = -0.31; total wake time and sleep duration variability: r = 0.31; sleep duration and sleep duration variability: r = -0.11). Further, variance inflation factors (VIF) were all well within the VIF < 5.0 range (VIF ranged from 1.05 – 1.14). Thus the effect of each variable on cognition was considered independent and it was deemed appropriate to move forward with the planned analyses (Craney & Surles, 2002; Farrar & Glauber, 1967; Tsui et al., 1995).

Participant characteristics are reported in Table 1. The two groups did not differ on any demographic characteristic with the exception of age; the BD-CONTROL group was significantly younger than the BD-INSOMNIA group ($p < 0.01$). There were also no significant group differences for the mood variables of current manic symptoms, illness duration, or number of mood episodes. The BD-INSOMNIA group reported significantly greater severity of depressive symptoms as indicated by average IDS-C scores ($p < 0.05$). In terms of psychotropic mediations, the BD-INSOMNIA group reported higher rates of antidepressant and hypnotic use ($p<0.001$) but less mood stabilizer use ($p < 0.001$) than the BD-CONTROL group. Moreover, BD-CONTROL participants reported a lack of any medication use more frequently than the BD-INSOMNIA group ($p < 0.05$). Finally, there were expected differences for the sleep variables, with the BD-INSOMNIA group consistently reporting more disturbed sleep on the ISI ($p<0.001$) and PSQI ($p<0.001$), and more insomnia symptoms as assessed by the sleep diary (i.e., total wake time = $p<0.01$, number of awakenings = $p<0.05$, and sleep efficiency = $p<0.01$). Sleep variables that did not significantly differ between groups were average bedtime, average wake time, duration of early morning awakenings, sleep duration, and all the sleep variability variables.

Primary Data Analyses

First Aim: Do insomnia diagnosis and insomnia-related sleep disruptions have an independent or interactive effect on cognition?

Results from the first aim are displayed in Table 2. After covarying age, there was a main effect of total wake time and sleep duration variability. Regardless of insomnia diagnosis, greater total wake time significantly predicted poorer working memory performance ($p<0.05$). Greater sleep duration variability, regardless of insomnia diagnosis, significantly predicted poorer verbal learning ($p<0.01$) and working memory performance ($p<0.05$).

Second Aim: Does cognition improve as sleep improves following CBTI-BD?

The results for second aim are presented in Table 3. Hierarchical linear regressions demonstrated a significant interaction between treatment group and reduction in total wake time with respect to improvement in working memory performance. Follow-up bivariate correlation analysis revealed that reduction in total wake time is associated with improvement in working memory performance in the CBTI-BD group (r=0.43). There was also a significant interaction between treatment group and reduction in sleep duration variability when examining improvement in verbal learning performance ($p<0.05$). A follow-up bivariate correlation examining the relationship between improvement in verbal learning and reduction in sleep

variability in the CBTI-BD group indicated a positive relationship (r=0.40*)*. There was also a main effect of sleep duration when examining improvement in verbal learning. More specifically, regardless of treatment group, a decrease in sleep duration was associated with an improvement in verbal learning performance ($p<0.01$).

DISCUSSION

Sleep disturbance and cognitive dysfunction are common during the inter-episode phase of bipolar disorder, with each contributing to impaired functional outcome and decreased quality of life (e.g., Boland et al., 2015; Harvey et al., 2005; Robinson et al., 2006). Despite evidence demonstrating the importance of sleep for cognition in healthy (e.g., Yoo et al., 2007) and sleep-disturbed samples (e.g., Orff et al., 2007; Varkevisser et al., 2007), this association has been minimally examined during inter-episode bipolar disorder. The overarching goal of the present study was to examine the impact of insomnia diagnosis and insomnia-related sleep disruptions on working memory and verbal learning performance during the inter-episode phase.

The first aim was to examine whether insomnia diagnosis and the insomnia-related sleep disruptions of total wake time, sleep duration, and sleep duration variability have an independent or interactive effect on working memory and verbal learning performance. There were two competing hypotheses for this aim and the results were consistent with the second hypothesis, which posited that greater total wake time, shorter sleep duration, and greater sleep duration variability would independently predict poorer cognitive performance, regardless of insomnia diagnosis. Indeed, we found that greater total wake time predicted poorer working memory performance and greater sleep duration variability predicted poorer working memory and verbal learning performance, regardless of diagnostic group status. Insomnia diagnosis did not predict working memory or verbal learning performance. This is consistent with the literature demonstrating no differences in objective cognitive performance when comparing an insomnia sample to healthy sleepers (Drummond et al., 2013; Orff et al., 2007; Varkevisser et al., 2007) Instead, results from the present study suggest that there are certain sleep disruptions common to insomnia *and* the inter-episode phase of bipolar disorder – more specifically fragmented sleep (i.e., total wake time) and inconsistent sleep duration across the week (i.e., sleep duration variability) – that are related to cognition. These results build upon previous studies which have demonstrated that fragmented sleep is associated with poorer cognition in older adults (Blackwell et al., 2006; Blackwell et al., 2014; Naismith et al., 2010; Wilckens et al., 2015) by demonstrating that fragmented sleep is associated with cognition during the inter-episode phase. Further, these results are the first to demonstrate an association between sleep duration variability and cognition and suggest that future studies should include measures of sleep duration variability when assessing the association between sleep and cognition.

Consistent with our hypothesis, results pertaining to the second aim demonstrated that an improvement in the sleep variables of interest (i.e., total wake time, sleep duration, and sleep duration variability) were associated with an improvement in cognition following CBTI-BD. More specifically, following CBTI-BD, (a) reduction in total wake time was associated with an improvement in working memory and (b) reduction in sleep duration variability was associated with an improvement in verbal learning. These results demonstrate that not only is baseline sleep duration variability and total wake time associated with impaired cognition, but stabilization of these sleep disruptions is also related to improvement on cognitive tasks. Taken together, the results from both aims suggest that total wake time and sleep duration variability may be two possible mechanisms underlying cognitive dysfunction in bipolar disorder. Moreover, these

results further highlight the importance of treating sleep disturbance during the inter-episode phase.

There were several surprising and noteworthy results. The first is the relationship between sleep duration and cognition during inter-episode bipolar disorder. Results the second aim demonstrated that a *decrease* in sleep duration following CBTI-BD and PE was associated with an improvement in verbal learning ($p<0.01$). One possible explanation for these results is that studies of habitual sleep suggest a U-shaped association between sleep duration and cognition whereby receiving fewer than 6 hours of sleep nightly or more than 9 hours of sleep nightly are both associated with cognitive impairment (Ferrie et al., 2011; Kronholm et al., 2009). Given the prevalence of hypersomnia and long sleep duration during inter-episode bipolar disorder (Kaplan et al., 2011; Kaplan et al., 2015; Ritter et al., 2012), it is possible that this result is being driven by *long-sleepers* (>9 hours per night). More specifically, in this subset of people, receiving *less* sleep may be beneficial for cognitive performance. There were too few long-sleepers in the BD-INSOMNIA group to test this hypothesis (N=5). However, when examining differences in sleep duration from pre-treatment to post-treatment assessment, the long-sleepers had the largest decrease in sleep duration and slept an average of 61.9 minutes fewer at the post-treatment assessment (compared to a 8.6-minute decrease in the average sleepers and a 86.5-minute increase in the short sleepers). Thus, this large decrease in sleep duration from pre- to post-treatment in the long-sleepers may be partially driving the result. A second noteworthy finding was that there were no significant between group differences for variability of sleep diary parameters (see Table 1). This suggests that circadian and sleep instability is inherent to bipolar disorder, regardless of insomnia diagnosis (e.g., Levenson & Frank, 2011; Ng et al., 2015).

Results from this study should be interpreted in light of several limitations. First, we did not covary for the use of psychotropic medications. Notably, side effects of psychotropic medications (e.g., cognitive impairment) often wear off or diminish as people continue on a medication course (Ketter & Wang, 2002) and participants in this study were required to be on a stable medication regimen for at least four weeks prior to study enrollment. Also, the literature examining the relation between psychotropic medication use and cognition in bipolar disorder is mixed with multiple studies demonstrating no association between the two (Altshuler et al., 2004; Arts et al., 2011; Lopez-Jaramillo et al., 2010; O'Shea et al., 2010; Thompson, 1991; Torrent et al., 2011). Consistent with these reports, our preliminary analyses demonstrated no link between psychotropic medication use and cognition, with the exception of mood stabilizer use, which was associated with better verbal learning performance. We highlight that research on medication-free bipolar samples is unrepresentative and lacks generalizability (Philips, Travis, Fagiolini, & Kupfer, 2008). A second limitation is that we did not have an insomnia group without a diagnosis of bipolar disorder or a healthy comparison group. Results from this study could have been strengthened by comparing cognitive performance in the BD-INSOMNIA group to an insomnia sample and cognitive performance in the BD-CONTROL group to a healthy control sample. Future studies should consider utilizing this study design.

Despite these limitations, this study contributes to the literature by demonstrating that insomnia-related sleep disruptions are related to deficits in working memory and verbal learning performance during the inter-episode phase of bipolar disorder. Given the functional impairment associated with both sleep disturbance and cognitive dysfunction, this study further highlights the importance of treating sleep disturbance during the inter-episode phase.

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Table 1. Baseline Demographic and Clinical Characteristics of the BD-INSOMNIA Group and BD-CONTROL Group

	BD-INSOMNIA (n=47)	**BD- CONTROL** (n=19)	**Statistical Test**
Demographic Information			
% Female	63.0%	65.2%	$\chi^2(1) = 0.04$
Age (mean years ± SD)	36.76 ± 11.23	30.74 ± 10.06	$t(64) = 2.22$*
Education (mean years ± SD)	15.67 ± 4.39	15.03 ± 5.70	$t(64) = 0.49$
Ethnicity			
% Hispanic or Latino	12.78%	13.04%	$\chi^2(1) = 0.25$
% Not Hispanic or Latino	85.11%	86.96%	$\chi^2(1) = 0.06$
Race			
% American Indian/Alaska Native	1.85%	0.00%	$\chi^2(1) = 0.43$
% Asian	9.26%	4.35%	$\chi^2(1) = 0.25$
% African American	11.11%	13.04%	$\chi^2(1) = 0.06$
% Caucasian	66.67%	52.17%	$\chi^2(1) = 1.42$
% Bi-racial	7.40%	14.39%	$\chi^2(1) = 1.73$
% Declined to Answer	3.70%	0.00%	$\chi^2(1) = 0.88$
Mood Variables			
IDS-C (mean score ± SD)	8.26 ± 6.90	5.17 ± 4.20	$t(64) = 1.99$*
YMRS (mean score ± SD)	3.81 ± 3.24	3.13 ± 3.11	$t(64) = 0.85$
Illness Duration (mean years ± SD)	15.19 ± 9.97	11.44 ± 7.41	$t(64) = 1.46$
# Mood Episodes	11.93 ± 13.61	7.06 ±5.38	$t(64) = 1.47$
# Manic Episodes (mean ± SD)	5.55 ± 6.27	3.00 ± 2.11	$t(64) = 1.68$
# Depressive Episodes (mean ± SD)	6.38 ± 8.37	4.06 ± 3.89	$t(64) = 1.13$
Psychotropic Medication Use			
% Mood Stabilizers	17.24%	60.87%	$\chi^2(1) = 14.73$***
% Antidepressants	53.44%	13.04%	$\chi^2(1) = 10.30$***
% Antipsychotics	65.52%	43.48%	$\chi^2(1) = 3.52$
% Anxiolytics	0.00%	4.35%	$\chi^2(1) = 2.49$
% Hypnotics	60.34%	0.00%	$\chi^2(1) = 23.76$***
% Anticonvulsant	56.90%	4.35%	$\chi^2(1) = 15.81$***
% Stimulants	12.07%	0.00%	$\chi^2(1) = 3.14$
% No medications	5.17%	21.74%	$\chi^2(1) = 4.89$*
Sleep Variables			
ISI (mean score ± SD)	18.28 ± 4.31	3.83 ± 3.73	$t(64) = 14.00$***
PSQI (mean score ± SD)	10.59 ± 5.05	3.43 ± 2.15	$t(64) = 6.53$***
Sleep Diaries			
BT (mean ± SD)	0:11 ± 1.62	0:44 ± 1.41	$t(64) = 0.83$
WT (mean ± SD)	8:17 ± 2.06	8:36 ± 1.24	$t(64) = 0.69$
TWT (mean mins. ± SD)	98.03 ± 59.05	57.12 ± 37.94	$t(64) = 3.05$**
NWAK (mean number ± SD)	0.11 ± 2.16	0.93 ± 0.69	$t(64) = 2.49$*
TST (mean mins. ± SD)	433.39 ± 92.97	464.71 ± 67.68	$t(64) = 1.46$
SE (mean percentage ± SD)	81.52 ± 10.26	89.00 ± 7.31	$t(64) = 3.16$**
BT Variability (mean mins. ± SD)	67.83 ± 35.74	54.65 ± 31.85	$t(64) = 1.52$
WT Variability (mean mins. ± SD)	84.25 ± 59.75	62.34 ± 20.03	$t(64) = 1.68$
TWT Variability (mean mins. ± SD)	59.76 ± 47.41	37.46 ± 36.59	$t(64) = 1.97$
TST Variability (mean mins. ± SD)	95.83 ± 58.30	73.54 ± 36.51	$t(64) = 1.69$
SE Variability (mean mins. ± SD)	10.56 ± 8.08	7.19 ± 6.86	$t(64) = 1.72$

Note. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

BT=bedtime; WT=wake time; TWT=total wake time; NWAK=number of nocturnal awakenings; TST=total sleep time or sleep duration; SE=sleep efficiency.

Table 2. Working Memory and Verbal Learning Performance Predicted by Insomnia Diagnosis, Insomnia-related Sleep Disruptions, and Group BY Insomnia-related Sleep Disruptions, Adjusting for Participant Age

	Working Memory			Verbal Learning		
	B	SE	Beta	B	SE	Beta
Step 1: Participant Characteristics						
Age	-0.03	0.01	-0.42***	-0.03	0.01	-0.41**
Step 2: Insomnia Diagnosis						
R^2 Change			*0.01*			*0.02*
Age	-0.03	0.01	-0.45***	-0.04	0.01	-0.47**
Group	0.16	0.17	0.11	0.25	0.25	0.13
Step 3: Insomnia-related sleep disruptions						
R^2 Change			*0.15***			*0.10**
Age	-0.03	0.01	-0.52***	-0.04	0.01	-0.47***
Group	0.34	0.17	0.24	0.30	0.25	0.13
Total Wake Time	-0.01	0.01	-0.26*	0.01	0.01	0.14
Sleep Duration	-0.01	0.01	-0.21	-0.01	0.01	-0.08
Sleep Duration Variability	-0.01	0.01	-0.26*	-0.01	0.01	-0.31**
Step 4: Interaction						
R^2 Change			*0.02*			*0.01*
Age	-0.03	0.01	-0.49***	-0.03	0.01	-0.45***
Group	0.29	0.23	0.20	0.37	0.34	0.19
Total Wake Time	-0.01	0.01	-0.12	-0.01	0.01	-0.09
Sleep Duration	-0.01	0.01	-0.47	-0.01	0.01	-0.35
Sleep Duration Variability	-0.01	0.01	-0.64*	-0.01	0.01	-0.39*
Group X Total Wake Time	-0.01	0.01	-0.12	0.01	0.01	0.21
Group X Sleep Duration	0.01	0.01	0.26	0.01	0.01	0.28
Group X Sleep Duration Variability	0.01	0.01	0.40	0.01	0.01	0.10

Values reported are unstandardized coefficients (B), standard error of B (SE), standardized regression coefficients (Beta) with significance of t and R^2 changes with significance of F.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Table 3. Improvements in Working Memory and Verbal Learning Performance Predicted by Treatment Group, Reductions in Total Wake Time, Increase in Sleep Duration, and Reduction in Sleep Duration Variability, Adjusting for Participant Age

	Improvement in Working Memory			Improvement in Verbal Learning		
	B	SE	Beta	B	SE	Beta
Step 1: Participant Characteristics						
Age	0.05	0.05	0.19	0.01	0.05	0.02
Step 2: Treatment Group						
R^2 Change			*0.04*			*0.04*
Age	0.05	0.05	0.19	0.01	0.05	0.05
Treatment Group (CBTI-BD vs. PE)	-1.11	0.97	-0.19	-1.35	1.11	-0.20
Step 3: Change in Insomnia-related Sleep Disruptions						
R^2 Change			*0.02*			*0.17*
Age	0.05	0.05	0.19	0.01	0.05	0.01
Treatment Group	-0.83	1.10	-0.14	-1.53	1.01	-0.23
Reduction in Total Wake Time (TWT)	-0.01	0.01	-0.04	-0.01	0.01	0.13
Increase in Sleep Duration (TST)	0.01	0.01	0.06	-0.02	0.01	-0.45**
Reduction in Sleep Duration Variability (TST var)	-0.01	0.01	-0.13	0.01	0.01	0.10
Step 4: Interactions						
R^2 Change			*0.20*			*0.14*
Age	0.01	0.05	0.03	0.01	0.05	0.01
Treatment Group	-0.75	1.04	-0.13	-1.96	1.07	-0.29
Reduction in Total Wake Time (TWT)	-0.02	0.01	-0.26	0.01	0.01	0.12
Increase in Sleep Duration (TST)	0.01	0.01	0.04	-0.01	0.01	-0.21
Reduction in Sleep Duration Variability (TST var)	0.01	0.02	0.03	-0.01	0.01	-0.17
Treatment Group X Reduction in TWT	0.06	0.02	0.49*	-0.01	0.03	-0.10
Treatment Group X Increase in TST	0.01	0.01	0.17	-0.02	0.01	-0.30
Treatment Group X Reduction TST var	-0.03	0.02	-0.28	0.05	0.02	0.44*

Values reported are unstandardized coefficients (B), standard error of B (SE), standardized regression coefficients (Beta) with significance of t and R^2 changes with significance of F.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$