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The Relationship between Sleep Quality and Neurocognition in Bipolar Disorder

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ABSTRACT

Backgrouns: Sleep and circadian rhythm disruptions are prominent, trait-like features of bipolar disorder (BD) which precede the onset of mood episodes. Neurocognitive impairments also characterize BD not only during acute phases of the illness but also during remission. Although the relationship between these two debilitating aspects of the illness might seem intuitive, very little is known about their relationship. We examined the association between sleep dysfunction and neurocognition in BD.

Methods: In a sample of 117 BD patients, neurocognitive functioning was assessed using the MATRICS Consensus Cognitive Battery (MCCB). Sleep quality data were collected using the Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI). Partial Pearson correlations tested for a relationship between sleep and neurocognition. Path analyses were conducted to examine the hypothesized direct influence of sleep disruption on neurocognition.

Results: Higher levels of sleep disruptions were associated with a more severe clinical presentation and poorer performance in social cognition, visual learning and working memory. Social cognition and working memory were directly (negatively) predicted by sleep disruptions.

Limitations: The study was limited by a relatively small sample size and the lack of behavioral and biological objectives measure of activity/rest cycles.

Conclusions: These results suggest that sleep disruptions are associated with a more severe clinical presentation in BD. Sleep disturbance and daytime dysfunction had a direct negative effect on social cognition. In addition, poor sleep quality negatively affected working memory. Mood symptoms only influenced cognitive functioning indirectly through their effects on sleep.

Key words: sleep disruption, sleep quality, neurocognition, bipolar disorder

INTRODUCTION

Bipolar disorder (BD) is characterized by fluctuating depression and mania with presumed inter-episode recovery; however, recent data clearly document that neither complete symptomatic remission nor functional recovery are the norm (Altshuler et al., 2002). Among the most persistent symptoms are circadian-based sleep and daytime activity abnormalities, often associated with anergia and psychomotor retardation (Mitchell and Malhi, 2004). Deficits in certain aspects of neurocognition are also common during remission (Golberg and Burdick, 2008). The presence of these continuing symptoms has a profound impact on quality of life, with a direct influence on clinical course and functional outcome (Marangell et al., 2009; Martínez-Arán et al., 2004).

Circadian Abnormalities in Euthymic BD: It has been long understood that changes in sleep and daytime activity/energy are cardinal features of acute mania and depression, with more recent data suggesting that these symptoms may represent trait-related risk factors for BD (Plante and Winkelman, 2008). Approximately 70% of remitted BD patients report diminished sleep efficiency and decreased daytime activity levels (Harvey et al., 2005). Euthymic patients with BD demonstrate increased sleep latency, a persistent pattern of insomnia and hypersomnia, and heightened sensitivity to shifts in circadian rhythms as compared with healthy controls (Ritter et al., 2012) and participants at increased risk for BD report a similar pattern, suggesting that circadian abnormalities represent a core illness feature that precede the onset of frank mood episodes.

A decreased *need* for sleep (maintenance of energy without adequate sleep) presents prior to the illness onset and during the prodromal period (Skjelstad et al., 2010). Unaffected offspring of BD patients demonstrate disrupted sleep/activity levels vs. controls without a family history (Ankers and Jones, 2009), supporting circadian abnormalities as a genetically-mediated feature of BD. Indeed, several genes that are known to regulate circadian functions (e.g. *CLOCK, PERIOD*) are risk loci for BD (Dallaspezia and Benedetti, 2009; Shi et al., 2008). A *CLOCK* gene polymorphism moderates features of the illness such as diurnal preference (Katzenberg et al., 1998), levels of evening activity, and delayed sleep onset in BD (Benedetti et al., 2007). The same variant has been linked with anterior cingulate activation in BD patients performing an emotional decision-making task (Benedetti et al., 2008). These convergent data suggest that biological rhythm abnormalities are core features of BD implicated in its pathophysiology.

Importantly, data suggest that impaired sleep quality in BD is associated with reduced quality of life. Gruber et al. (2004) assessed the relationship between sleep and clinical features in 2024 BD patients enrolled in NIMH STEP-BD (Gruber et al., 2004). Abnormal sleep duration was associated with poor functional outcome and quality of life. Patients with BD report significant anxiety related to their sleep, and cite circadian stability as an important goal of treatment (Ritter et al., 2012; Suto et al., 2010). In a study of 21 *euthymic* BD patients, sleep inefficiency and variability in total wake-time were associated with a greater number of lifetime depressive episodes and higher levels of current subthreshold depression and mania (Eidelman et al., 2010). Even subtle changes in sleep-wake patterns in BD can result in rapid destabilization and the onset of acute episodes (Plante and Winkelman, 2008). These data support the need to normalize biological rhythms to improve clinical status and quality of life in patients with BD.

Cognitive Impairment in BD: In addition to chronic neurovegetative symptoms, many BD patients are cognitively impaired during euthymia, particularly in the domains of attention, verbal memory, and executive functioning (Arts et al., 2008; Bowie et al., 2010; Golberg and Burdick, 2008). Moreover, similar to the effects of sleep disruption on quality of life, persistent cognitive deficits contribute significantly to functional disability in BD (Bowie et al., 2010), making them a critical treatment target for future studies (Burdick et al., 2012, 2007).

Relationship between Circadian and Cognitive Impairment in BD: The relationship between sleep quality, daytime wakefulness, and neurocognition seems intuitive, with sleep deprivation resulting in lower energy and impaired cognition in animals and humans (Gerstner et al., 2009). Although few studies have assessed the possible association between circadian and cognitive dysfunction in BD, given their persistent impairment during euthymia and what is known from prior work in other clinical samples, it is reasonable to assume that they are closely linked. A study evaluated the deleterious cognitive effects of biological rhythm disruption in BD and demonstrated that circadian disruption is highly prevalent (approximately 80%) in inter-episode patients and that sleep disruption was the strongest predictor of everyday function including work and social outcome (Giglio et al., 2010). Moreover, although only a single task of executive functioning was administered, results indicated significant correlations between performance on this measure and biological rhythms. Likewise, a recent study reported that BD patients with more severe cognitive dysfunction report higher rates of insomnia compared to patients with

intact cognitive functioning (Volkert et al., 2015). Although in this latter study the sleep disruptions were evaluated by using a non-sleep specific measure (rather from a depressive symptom rating scale) the results support the presence of an association between sleep disruption and cognitive dysfunction in BD (Volkert et al., 2015).

Taken together, these data suggest that these commonly co-occurring symptoms in remitted BD may be directly linked with one another. A better understanding of their relationship may shed light on a shared neurobiology and point toward novel pharmacological and psychotherapeutic strategies that could successfully target both domains simultaneously. In an effort to evaluate this relationship, we have assessed a cohort of stable BD patients on measures of sleep dysfunction, daytime sleepiness, and cognitive functioning and have tested the hypothesis that core bipolar disorder symptomatology and sleep disruptions would have both direct and mediating effects on cognitive functioning.

METHODS

Participants

The sample was composed of 117 BD outpatients from two sites: 89 patients from the Icahn School of Medicine at Mount Sinai and 28 from the Zucker Hillside Hospital – North Shore Long Island Jewish Health System (NSLIJHS). Inclusion criteria were: 1) Diagnosis of BD I or BD II or BD NOS; 2) 18-65 years old; 3) Current affective stability as measured by a score of less than 15 on the Hamilton Rating Scale for Depression [HRSD; (Hamilton, 1967)] and a score of less than 8 on the Clinician Administered Rating Scale for Mania [CARS-M; (Altman et al., 1994)]. Exclusion criteria were: 1) history of CNS trauma, neurological disorder, and ADHD or Learning Disability diagnosed in childhood; 2) diagnosis of recent substance abuse/dependence (past 3 months); 3) active, unstable medical problem; 4) ECT in the past 12 months. All procedures were approved by the local IRB and written informed consent was obtained from all participants.

Clinical Measures

DSM-IV diagnosis of BD was ascertained and confirmed by a consensus panel using the Structured Clinical Interview for DSM-IV (SCID). Numbers of life-time mood episodes were collected during the diagnostic

interview; current depressive and manic symptoms were evaluated using the HRSD and the CARS-M. Severity of general psychiatric symptoms was assessed through the Brief Psychiatric Rating Scale [BPRS; (Pull and Overall, 1977)] and trait levels of impulsivity were measured using the Barratt Impulsiveness Scale [BIS-11; (Patton et al., 1995)].

Neurocognitive and Affective Processing Measures: The MATRICS Consensus Cognitive Battery [MCCB; (Nuechterlein et al., 2008)] was used to evaluate neurocognitive performance. The MCCB includes several tests that give rise to 7 cognitive domains: 1) Processing Speed [Brief Assessment of Cognition in Schizophrenia (BACS) and Trail Making Test part A]; 2) Attention/Vigilance [Continuous Performance Test—Identical Pairs (CPT-IP)]; 3) Working Memory [Wechsler Memory Scale (spatial and letter-number span)]; 4) Verbal Learning [Hopkins Verbal Learning Test—Revised (HVLT-R)]; 5) Visual Learning [Brief Visuospatial Memory Test—Revised (BVMT-R)]; 6) Reasoning and Problem Solving [Neuropsychological Assessment Battery (NAB) Mazes subtest]; and 7) Social Cognition [Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT)]. The battery takes approximately 70 minutes to complete and testing was done in a single session. Scores are expressed in t-scores with a mean of 50 and a standard deviation (SD) of 10. The Wide Range Achievement Test (WRAT)-3 (Wilkinson, 1993) was used to obtain the estimated premorbid intelligence.

Sleep/Activity Assessment: The Epworth Sleepiness Scale [ESS(Johns, 1991)] and the Pittsburgh Sleep Quality Index [PSQI; (Buysse et al., 1989)] were used to evaluate daytime wakefulness and sleep quality.

The ESS is a self-report questionnaire that measures daytime sleepiness/wakefulness. Subjects rate the probability of falling asleep on a scale of increasing probability from 0 to 3 in eight situations (e.g. sitting and reading, watching TV, talking to someone, or in car as a passenger). The ESS total score (ESS Total) ranges from 0 to 24.

The PSQI is a self-report instrument measuring the quality and pattern of sleep in adults. It is not intended for the diagnosis of sleep disorders, but rather to identify ‘good’ and ‘bad sleepers’. Subjects rate their sleep habits within the past month by reporting the frequency with which a specific sleep habit occurs. The test gives rise to 7 subscales (Sleep Duration, Sleep Disturbances, Sleep Latency, Daytime Dysfunction, Sleep Efficiency, Overall Sleep Quality and Use of Sleeping Medication), of which we were most interested in the functionally-relevant subscales measuring sleep disturbances and daytime dysfunction and overall sleep quality (PSQI Total). Scores range from 0 to 3 for the subscales and from 0 to 21 for the total PSQI score. For both the ESS and PSQI *higher scores* indicate *more severe* sleep disruption.

Statistical Analyses

The associations between sleep measures (total score obtained from the ESS, the PSQI total and subscale scores) and both age and clinical data (depressive and manic symptoms, premorbid IQ, level of general psychopathology and impulsiveness) were tested using univariate analysis of variance (ANOVA) and bivariate Pearson correlations where appropriate. Bivariate Pearson correlations were used to describe potential associations between sleep disruptions (ESS and PSQI scores) and neurocognition (MCCB domains). Significant (*p value* <.05) and trend-level correlations (*p value* < .10) were followed up using a series of path analyses to test the direct and indirect relationships between clinical symptoms, sleep disruption and neurocognitive functioning.

Path analysis is a statistical technique that tests hypotheses about the causal connections between a set of variables. Model selection was done through an iterative procedure. Starting from a saturated model (where all variables are interrelated), we gradually excluded those pathway correlations that are not significant until a good-fitting model was reached. Goodness of fit was assessed by examining three indices: the Chi-square, the Comparative Fit Index (CFI) and the Root Mean Square of Error Approximation (RMSEA). A good model is defined by a not significant Chi-Square test (*p* value ≥.5), a CFI equal or higher than .9 and a RMSEA lower or equal to .6. A ratio of five cases to each parameter in the path analysis is necessary for appropriate statistical power. Our saturated models included no more than 25 parameters, therefore statistical power with a sample of 117 was considered satisfactory.

The model was structured such that the direct and indirect effects of clinical symptoms (symptoms of mania and depression as well as trait impulsivity; top tier of model) and sleep quality (second tier) on cognition (third tier) could be tested.

RESULTS

The mean age of the participants was 45.0 (SD= 10.7), 59.0% (*n*=69) were males; and 27.4% (n=32) were Caucasian. The mean premorbid IQ (WRAT-3) was 96.1 (SD=13.7), indicating normal intellectual functioning. The mean score for current depressive symptoms (HRSD total) was 9.7 (SD=8.4) and the mean rating for manic symptoms (CARS-M total) was 4.5 (SD=5.6), consistent with affective stability. The average rating for general psychopathology (BPRS total) was 24.1 (SD=6.1). Eighty-two patients had a diagnosis of BD I [*n*=32 (27.4%) with psychotic features]; 28 patients had a diagnosis of BD II ([*n*=8 (6.8%) with psychotic features]; and 7 patients (6.0%) had a diagnosis of BD NOS. The mean number of manic and hypomanic episodes was 12.9 (SD= 14.1); the mean number of depressive episodes was 14.5 (SD=15.1). Level of general impulsivity, as assessed by the BIS-11, was 70.3 (SD=11.3). As reported in **Table 1** scores on the MCCB domains ranged around 1 SD below the mean of the general population, with poorest performance in the Working Memory Domain (mean T-score =38.4; SD=12.9).

Sleep Measures. Subjects had a mean ESS total score of 9.2 (SD= 4.9), which was significantly correlated with the PSQI day dysfunction (*r*=.224; p=.018) and the PSQI sleep disturbance (*r*=.250; p=.008) subscales from the PSQI. Scores on the ESS [(based upon normative data from a non-psychiatric sample without sleep disorders (Sanford et al. 2006)] showed that BD subjects in our sample reported negligible daytime sleepiness (mean z-score=-.19 +/-1.8; **Table 1**). Conversely BD subjects compared to normative US population (Sanford et al., 2006) reported severe impairment on the day dysfunction (z=-2.0+/-1.7) and sleep disturbance PSQI subscales (z=-1.7+/-1.8) with an overall level of sleep quality (PSQI total score) well below the mean of the healthy population (z=-3.8+/-2.6; **Table 1**). Indeed 85.7% of the BD subjects reported day dysfunction and all but one of the subjects (97.3%) reported sleep disturbance.

More severe sleep disruptions were associated with an overall more severe clinical presentation (**Supplemental Material 1**). *Although patients were affectively stable at the time of assessment* several associations with severity of subthreshold symptoms and sleep measures emerged. More severe depressive symptoms were associated with greater impairment on PSQI sleep disturbance (r =.223, p =.018) and PSQI day dysfunction (r =.335, p<.001). Likewise, a higher level of general psychopathology was also associated with greater impairment on sleep disturbance (r =.260, p =.005) and day dysfunction (r =.244, p =.010). Impairment on the sleep disturbance subscale was also associated with more severe manic symptoms (r =.326, p <.001), lower premorbid IQ (r =-.238, p =.013) and higher impulsivity (BIS Total score; r =.310, p =.001). The PSQ total score was strongly associated with more severe depression (r =.449, p<.001) and mania (r =.214, p=.022).

Neurocognition and Sleep Disruption. Correlational analyses indicated significant associations between cognitive performance and sleep disruptions (**Figure 1; Supplemental Material 1**). Performance on social cognitive measures was negatively associated with ESS total (daytime sleepiness; r=-.251, p =.008), PSQI sleep disturbance (r =-.273, p =.004), and PSQI day dysfunction (r =-.330, p<.001). Performance on a visual learning measure was also associated with ESS daytime sleepiness (r =-.247, p =.009). We found trend-level relationships between working memory performance and ESS daytime sleepiness (r=-.184, p =.052), PSQI sleep disturbance (r=-.179, p=.061) and PSQ total score (r=-.168, p=.078). Trend-level associations were also noted between visual learning performance and PSQI sleep disturbance (r=-.161, p=.094); and between social cognition and PSQ total score (r=-.162, p=.089). Based upon these correlational results we tested three potential models using pathway analyses to evaluate whether these aspects of cognition can be predicted by clinical symptomatology (depressive/manic symptoms, and impulsivity) and/or sleep disruption and to begin to address the direction of these relationships.

Path analyses supported good-fit predictive models for social cognition and working memory (indices of fit statistics reported in **Table 2**); however, the visual learning model did not achieve an adequate fit. Social cognition was directly predicted by PSQI sleep disturbance (regression weight=-.19) and PSQI day dysfunction (regression

weight=-.29), while clinical symptoms only influenced cognition through an indirect pathway via their effects on sleep (i.e. impulsivity and manic symptoms directly influenced PSQI sleep disturbance and depressive symptoms had direct effects on PSQI day dysfunction). PSQI sleep quality had direct effects on working memory performance (PSQ total score; regression weight=-.27) and impulsivity had both direct (regression weight=.26) and indirect (via effects on PSQI sleep quality) effects on working memory. Depression indirectly impacted working memory via effects on PSQI sleep quality (direct and total standard effect are presented in **Supplemental Material 2**).

To assess the directionality of our hypothesis and results, we also tested the reverse hypothesis that cognitive impairment in BD might be driving the expression of sleep or cognitive problems via direct or indirect effects on clinical symptomatology and sleep disruption. We tested an alternate model wherein cognition served as the endogenous variable influencing clinical symptoms and sleep disruption. As expected, this model was not statistically meaningful and was therefore rejected.

DISCUSSION

To our knowledge, this study is among the first to directly investigate the relationship between sleep disruption and neurocognition in BD. Our findings corroborate previous data noting sleep disruption as a prominent feature of BD (Harvey et al., 2005) and extend prior work to suggest that more severe cognitive impairment in BD is associated with higher rates of sleep dysfunction (Volkert et al., 2015). Data from the PSQI, which measures a broad range of sleep dimensions, suggest that the vast majority of patients with BD report major sleep disruptions even during affective remission. We further found that more severe sleep disruptions were associated more severe clinical symptoms and with lower premorbid IQ.

Next we explored the relationship between sleep dysfunction and neurocognition and found, as might be expected, that more severe sleep disruptions were associated with poorer cognitive performance. Specifically, performance on measures of working memory, visual learning, and social cognition was correlated with patient ratings of sleep quality (PSQI) and daytime sleepiness (ESS). When we applied path analyses to these

variables in an effort to determine directionality of the relationships, we found valid predictive models for both working memory and social cognition. Working memory performance was best predicted by direct effects of sleep quality (PSQI total) and trait impulsivity (BIS-11). While the deleterious effects of poor sleep quality on cognition seems intuitive, the effects of impulsivity in this model are somewhat counterintuitive as they have a positive weight, suggesting a potential beneficial effect of higher trait impulsivity on working memory in our patients with BD. Social cognitive performance was best predicted by direct effects of sleep disturbance and day dysfunction, with no direct effects attributed to any of the clinical symptoms. Current severity of affective symptoms only contributed to social cognitive performance via their effects on sleep quality (**Figure 2**).

Together, these results suggest that sleep disruption and cognitive functioning may share a common neuropathological mechanism in BD. Previous studies in healthy subjects have demonstrated that once sleep is recovered following deprivation, energy and activity levels return to baseline and normal cognition is restored (Benca et al., 2009); however, the persistent nature of sleep abnormalities in BD suggests a more chronic circadian disruption. In preclinical work, Craig and McDonald (Craig and McDonald, 2008) demonstrated hippocampus-based learning and memory deficits in rats that were exposed to repeated phase shifts and recoveries but no such deficit in rats who underwent only acute phase shift and recovery, suggesting that it may be the chronicity of the circadian disruption that leads to the persistent cognitive dysfunction seen in the remitted phase of BD.

The specific nature of the circadian abnormality in BD is not known; however, Dallaspezia and Benedetti described two related hypotheses: 1) Patients with BD have a biological clock that is detached from environmental variables that act to regulate circadian rhythms; and/or 2) The normal sleep-wake cycle in BD is not in phase with other biological rhythms (e.g. melatonin release) (Dallaspezia and Benedetti, 2009). Data in BD support a high rate of an “eveningness” chronotype, a preference for later bedtimes/wake-times, and for carrying out mental and physical activity in the evening as opposed to the morning (Volkert et al., 2015; Wood et al., 2009). Eveningness is associated with a circadian phase delay, a shift in the normal temperature reduction and melatonin secretion that triggers onset of the circadian-based sleep cycle, as well as waking times that are

misaligned to circadian phase (Duffy et al., 1999). Such circadian desynchronization results in elevated melatonin, a sleep-promoting hormone, early in the day thereby impairing wakefulness and vigilance.

The potential to target sleep dysfunction and neurocognitive impairments using either pharmacological approaches or therapy will be an important consideration moving forward. There is not yet an effective class of medications able to target both deficits simultaneously. However, there are encouraging data suggesting that wake-promoting drugs that increase dopamine and serotonin activity in the cortex (e.g. modafinil) may have an enhancing effect on cognition in healthy, sleep-disordered and other psychiatric disorders (Minzenberg and Carter, 2008). Psychosocial interventions that incorporate psychoeducation and careful monitoring of social rhythms and sleep patterns, particularly Interpersonal Social Rhythms Therapy (IPSRT), have also been shown to be effective in reducing episode recurrence in BD over 2-years (Frank et al., 2005).

The main limitation of this study is the relatively small sample size. Future studies will require additional subjects to be evaluated and our current results should be replicated and extended. Specifically, the adoption of behavioral (actigraphy) or biological measures [melatonin; cortisol] to objectively measure activity/rest cycles and critical hormones will be important in clarifying the nature of the circadian abnormalities and their relationship with cognition in BD.

In summary, sleep disruption adversely influences neurocognition in BD. We provide statistical evidence to suggest that sleep problems may be driving neurocognitive impairments in BD, at least in some domains (working memory and social cognition). Further research using longitudinal designs and in individuals at risk for bipolar disorder will be important in establishing a causal relationship among these disabling aspect of the illness.

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Table 1. Cognitive Performance, Mean Score of Daytime Sleepiness (ESS) and Sleep Quality (PSQI) in BD Patients

MATRICS Cognitive Consensus Battery (MCCB)	**Mean T-score**	**SD**
Processing Speed (n=112)	41.1	11.6
Attention and Vigilance (n=110)	40.1	11.7
Working Memory (n=113)	38.4	12.9
Verbal Learning (n=55)	39.1	7.7
Visual Learning (n=112)	39.9	12.9
Reasoning & Problem Solving (n=112)	42.0	9.4
Social Cognition (n=113)	41.3	11.8
	Mean z-score	**SD**
Epworth Sleepiness Scale (ESS; Daytime Sleepiness; n=116)	-.19	1.19
Pittsburgh Sleep Quality Index (PSQI)		
Sleep Disturbance (n=113)	-1.7	1.8
Day Dysfunction (n=112)	-2.0	1.7
Sleep Quality Total Score (n=114)	-3.8	2.6

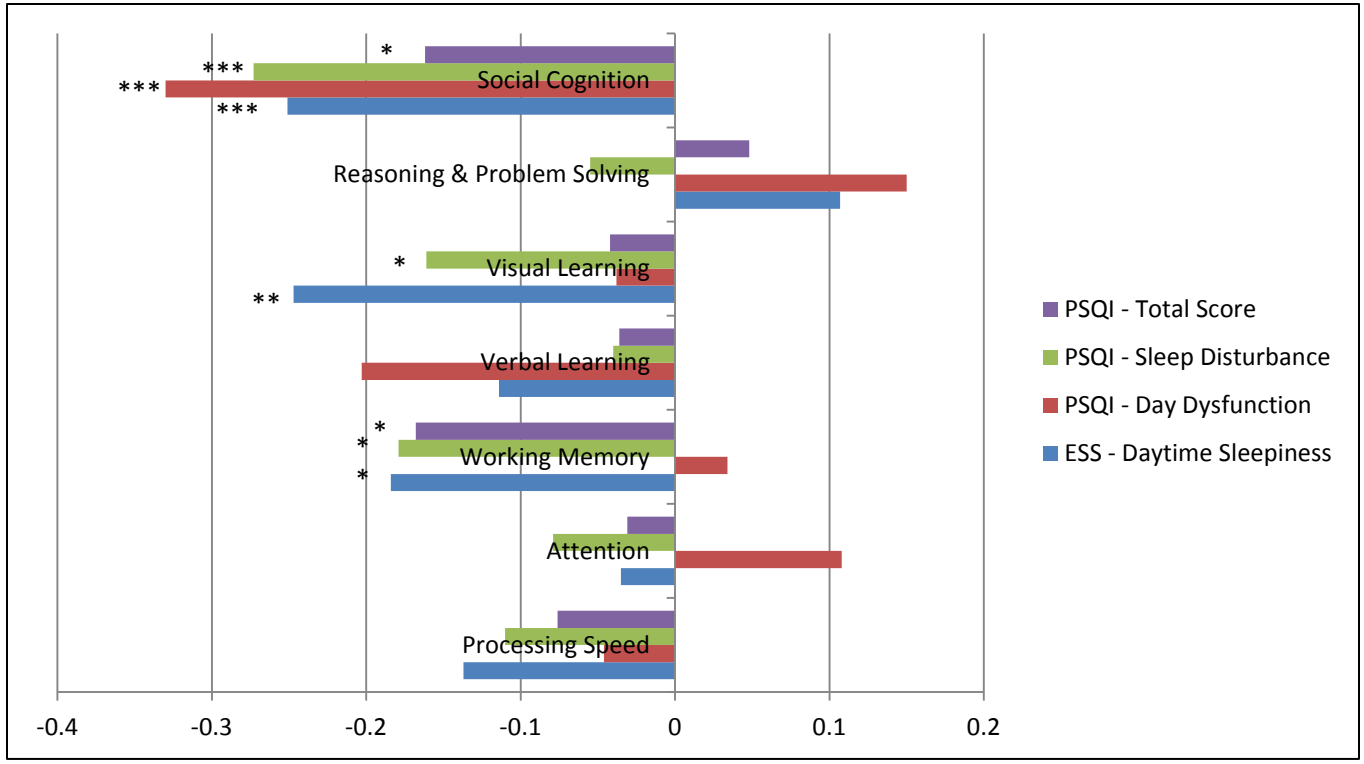
A negative mean score on both ESS and PSQI corresponds to a more severe sleep disruption

Table 2. Indices for the Final Model and the Independence Model[a] testing the Relationship between Clinical Symptoms, Sleep Disruption and Cognition in Bipolar Disorder

	Goodness of Fit				
Outcome Measure	**X^2**	**df**	**p value**	**CFI**	**RMSEA**
Working Memory					
Final Model	1.808	3	.613	1.000	.000
Independence Model	91.339	15	<.001	.000	.209
Social Cognition					
Final Model	9.501	7	.219	.969	.055
Independence Model	102.694	21	<.001	.000	.183

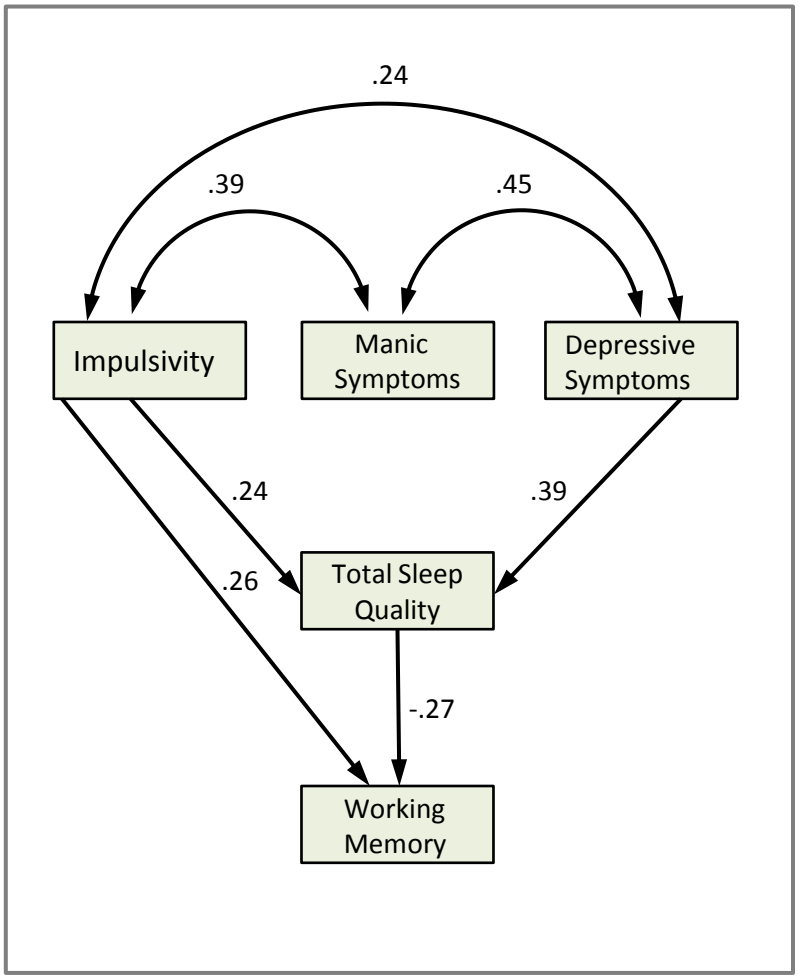
[a] The independence model is a null model that assumes that all the variables are uncorrelated with the dependent variable

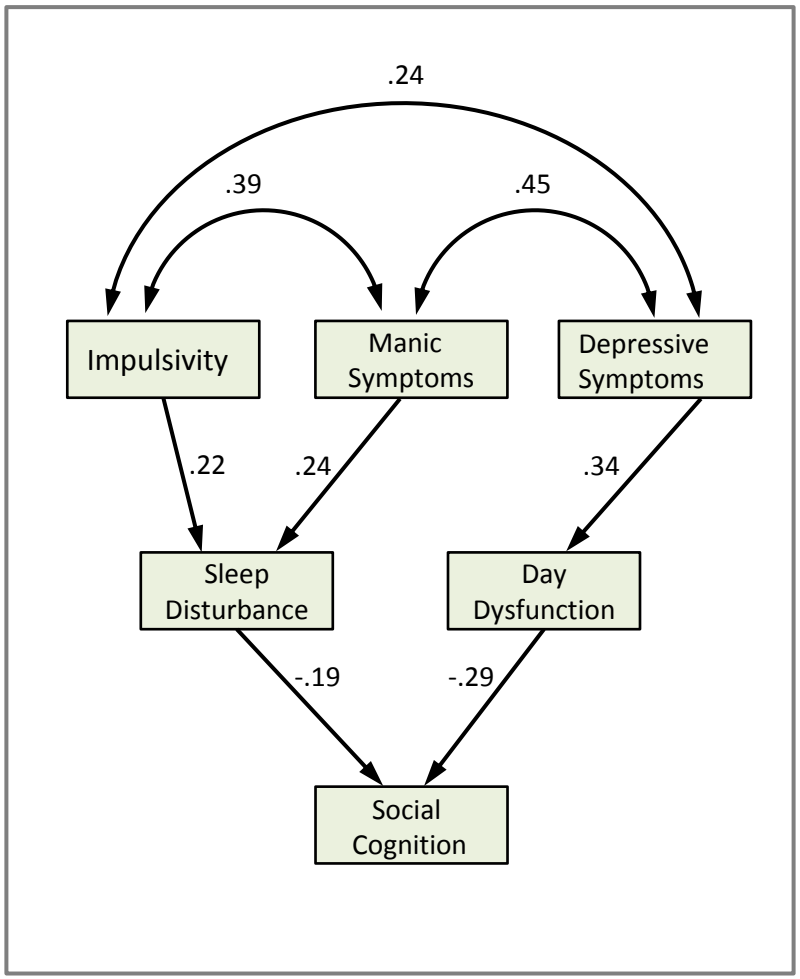
Figure 1. Bivariate Correlations between Cognitive Domains and Sleep Measures



*Note *p<.1; **p<.05; ***p<.01*

Figure 2 Prediction of Social Cognition (left) and Working Memory (right) with Clinical Symptoms and Sleep Disruptions in Bipolar Disorder





Supplemental Material 1. Association (Bivariate Correlation and ANOVA) between Sleep Disruptions in Bipolar Disorder Patients and Demographic/Clinical Characteristics and Cognition

	ESS- Daytime Sleepiness			PSQI- Sleep Disturbance			PSQI-Day Dysfunction			PSQI-Total Score		
	r	p value	N	r	p value	N	r	p value	N	r	p value	N
Age	-.043	.647	116	.040	.676	113	-.127	.183	112	.020	.883	114
Hamilton Rating Scale for Depression (HRSD) - 24	.077	.410	116	**.223**	**.018**	**113**	**.335**	**.000**	**111**	**.449**	**.000**	**113**
Clinician Administered Rating Scale for Mania (CARS-M)	.168	.071	116	**.326**	**.000**	**113**	.148	.119	112	**.214**	**.022**	**114**
Premorbid Intellectual Functioning (WRAT-3)	-.163	.087	111	**-.238**	**.013**	**108**	.023	.817	106	-.185	.054	109
General Level of Psychopathology (BPRS)	.058	.533	116	**.260**	**.005**	**113**	**.244**	**.010**	**112**	.175	.063	114
Number of Depressive Episodes	-.134	.226	83	-.104	.351	82	-.010	.927	81	.085	.446	83
Number of Manic Episodes	-.058	.606	81	-.073	.522	80	-.092	.420	79	-.032	.780	81
Impulsivity (BIS-11) Total Score	.127	.173	116	**.310**	**.001**	**113**	.157	.097	112	**.333**	**.000**	**114**
MCCB Domains												
Processing Speed	-.137	.150	112	-.110	.254	109	-.046	.642	107	-.076	.433	110
Attention	-.035	.718	109	-.079	.417	107	.108	.274	105	-.031	.752	108
Working Memory	**-.184**	**.052**	**112**	**-.179**	**.061**	**110**	.034	.727	108	**-.168**	**.078**	**111**

Verbal Learning	-.114	.410	54	-.040	.775	53	-.203	.158	50	-.036	.799	53
Visual Learning	**-.247**	**.009**	**112**	**-.161**	**.094**	**109**	-.038	.698	107	-.042	.666	110
Reasoning & Problem Solving	.107	.260	112	-.055	.571	109	.150	.123	107	.048	.618	110
Social Cognition	**-.251**	**.008**	**112**	**-.273**	**.004**	**110**	**-.330**	**<.001**	**108**	**-.162**	**.089**	**111**

Supplemental Material 2. Direct and Indirect Regression Weights

Outcome variable: Social Cognition		
	Standardized (direct) Regression Weight	**p value**
Impulsivity Sleep Disturbance	.215	.023
Manic Symptoms Sleep Disturbance	.237	.012
Depressive Symptoms Day Dysfunction	.339	.000
Sleep Disturbance Social Cognition	-.194	.030
Day Dysfunction Social Cognition	-.293	.001

Standardized Total Effects			
	Sleep Disturbance	**Day Dysfunction**	**Social Cognition**
Impulsivity	.215	.000	-.042
Depressive Symptoms	.000	.339	-.099
Manic Symptoms	.237	.000	-.046

Outcome variable: Working Memory		
	Standardized (direct) Regression Weight	**p value**
Impulsivity Sleep Quality	.237	.005
Depressive Symptoms Sleep Quality	.393	.000
Impulsivity Working Memory	.262	.006
Sleep Quality Working Memory	-.272	.005

Standardized Total Effects		
	Sleep Quality	**Working Memory**
Impulsivity	.237	.197
Depressive Symptoms	.393	-.107

Highlights

- Sleep disruptions in BD are correlated with a more sever clinical presentation;
- Higher levels of sleep disruptions are associated with a poorer performance in social cognition, visual learning and working memory;
- Our results suggest that social cognition and working memory were directly (negatively) predicted by sleep disruptions.