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Sleep architecture as correlate and predictor of symptoms and impairment in inter-episode bipolar disorder: taking on the challenge of medication effects

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SUMMARY This study was designed to clarify the association between inter-episode bipolar disorder (BD) and sleep architecture. Participants completed a baseline symptom and sleep assessment and, 3 months later, an assessment of symptoms and impairment. The effects of psychiatric medications on sleep architecture were also considered. Participants included 22 adults with BD I or II (inter-episode) and 22 non-psychiatric controls. The sleep assessment was conducted at the Sleep and Psychological Disorders Laboratory at the University of California, Berkeley. Follow-up assessments 3 months later were conducted over the phone. Results indicate that, at the sleep assessment, BD participants exhibited greater rapid eye movement sleep (REM) density than control participants with no other group differences in sleep architecture. Sleep architecture was not correlated with concurrent mood symptoms in either group. In the BD group, duration of the first REM period and slow-wave sleep (SWS) amount were positively correlated with manic symptoms and impairment at 3 months, while REM density was positively correlated with depressive symptoms and impairment at 3 months. The amount of Stage 2 sleep was negatively correlated with manic symptoms and impairment at 3 months. In contrast, for the control group, REM density was negatively correlated with impairment at 3 months. SWS and Stage 2 sleep were not correlated with symptoms or impairment. Study findings suggest that inter-episode REM sleep, SWS and Stage 2 sleep are correlated with future manic and depressive symptoms and impairment in BD. This is consistent with the proposition that sleep architecture may be a mechanism of illness maintenance in BD.

KEYWORDS bipolar disorder, rapid eye movement sleep, sleep architecture, slow-wave sleep, stage 2 sleep

INTRODUCTION

Individuals with bipolar disorder (BD) spend approximately 50% of their adult lives unwell, with the majority of this time marked by subsyndromal symptoms persisting into the inter-episode period (Judd *et al*., 2002). Sleep disturbance in the inter-episode period has been reported to be comparable to chronic insomnia and to have a prognostic value in BD (see Harvey, 2008 for review). For instance, decreased sleep has been found to be the most common prodrome of mania (Jackson *et al*., 2003) and to predict depressive symptoms at a 6-month follow-up (Perlman *et al*., 2006). Hence, the present study focused on inter-episode sleep disturbance as a mechanism that may contribute to impairment and be associated with future illness course. To the best of our knowledge, studies utilizing sleep disturbance as a predictor of symptoms

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and impairment in BD have relied on subjective perceptions of sleep (e.g. Perlman *et al*., 2006) or have experimentally induced sleep deprivation in the lab and observed next-day effects (Wehr *et al*., 1987). We aimed to extend past findings by evaluating the predictive value of objectively measured sleep architecture in inter-episode BD.

Increased rapid eye movement (REM) activity (i.e. shortened REM latency, longer duration of the first REM period, higher percentage of REM over the course of the night and greater REM density) has been widely reported in unipolar depression (e.g. Benca *et al*., 1992), and REM sleep has been proposed to have a mood-regulatory role that malfunctions in mood disorders (Cartwright *et al*., 1998). REM in BD has received less empirical attention than in unipolar depression, and the evidence is mixed. Patients with BD who are manic or depressed have been reported to exhibit decreased (e.g. Hudson *et al*., 1992), increased (e.g. Giles *et al*., 1986) or equivalent REM latencies (Jernajczyk, 1986) relative to healthy controls and to patients diagnosed with unipolar depression. In the inter-episode period, patients with BD have shown sleep marked by increased REM activity (Knowles *et al*., 1986) and sleep that does not differ from that of controls (Sitaram *et al*., 1982). Studies of healthy relatives of individuals diagnosed with a mood disorder point to the possibility that disturbances in REM sleep may be a marker of affective disorder vulnerability. Such studies suggest that the sleep of relatives of individuals diagnosed with unipolar depression or BD is marked by increased REM activity compared with controls (Giles *et al*., 1998; Modell *et al*., 2003). In addition, greater REM density has been found to distinguish those relatives who go on to experience an affective episode from unaffected relatives and controls (Modell *et al*., 2007).

Slow-wave sleep (SWS), which consists of Stages 3 and 4, is thought to have a restorative function in healthy individuals that includes memory consolidation and cell regeneration, and has been found to be decreased in unipolar depression (e.g. Benca *et al*., 1992). The two-process model of sleep regulation proposes that SWS is an index of the homeostatic process (Borbely, 1982), which may be weakened in depression (Borbely, 1987). Decreased SWS has also been reported in BD (Jovanovic, 1977) and in depressed adolescents who go on to have a BD illness course (Rao *et al*., 2002). However, most studies report SWS in mania and BD to be equivalent to that of healthy controls (Hudson *et al*., 1988, 1992; Jernajczyk, 1986; Mendelson *et al*., 1987). Thus, the manner in which SWS is disturbed in BD is unclear, particularly during the inter-episode period.

Stage 2 sleep is also thought to have an important restorative and sleep-protective function (De Gennaro and Ferrara, 2003; Hayashi *et al*., 2005). Although it is understudied in mood disorders, decreased Stage 2 sleep has been found in both unipolar and BD (de Maertelaer *et al*., 1987). Additionally, in studies of clozapine, treatment response in BD was most dramatically associated with the enhancement of Stage 2 sleep (Hinze-Selch *et al*., 1997).

The present study was designed to clarify the association between BD and REM, SWS and Stage 2 sleep. We aimed to investigate whether there is a cross-sectional association between symptoms and sleep architecture, and whether sleep architecture predicts symptoms and mood-associated impairment at 3-month follow-up in patients with BD during the inter-episode period relative to a non-psychiatric control group. Our first hypothesis was that higher levels of depressive and manic symptoms at the baseline sleep assessment would be associated with increased REM activity (shorter REM latency, higher REM%, longer duration of first REM, greater REM density), and that increased REM activity would be associated with higher levels of depressive symptoms, manic symptoms and impairment at 3-month follow-up. Second, we hypothesized that increased Stage 2 sleep would be associated with lower levels of manic and depressive symptoms, impairment at the baseline sleep assessment and at the 3-month follow-up. Given the mixed findings for SWS reported in the published reports, we included SWS on an exploratory basis.

Our third study aim relates to medication effects, an issue that increasingly requires consideration in neuroscience and psychological research on serious mental illness. A large majority of patients with BD are treated with polypharmacy (Ghaemi *et al*., 2006). Thus, if research is conducted on only medication-free participants, progress will be slow and the results may not be generalizable to the majority of patients with BD. Hence, our third aim was to devise an approach to medication effects that balances scientific rigor and clinical reality.

MATERIALS AND METHODS

Participants

Participants were recruited from advertisements and referrals targeting 'good sleepers' and 'individuals diagnosed with BD'. Of the 266 callers who were screened, 51 chose not to participate or could not be reached subsequently, 25 did not complete the protocol and a total of 146 were excluded from participating in either the BD or the control group. Participants were excluded from the BD group for: not being under psychiatric care (requirement of the ethics committee; $n = 23$); not meeting Structured Clinical Interview for DSM-IV (SCID-IV; First *et al*., 1994) diagnostic criteria for BD Type I or II ($n = 22$); and diagnosis of a current substance or alcohol abuse disorder ($n = 4$). In addition, participants were excluded from the BD group for not being inter-episode, as defined by: a score greater than 11 on the Clinician Rated Inventory of Depressive Symptomatology (IDS-C; Rush *et al*., 1996); a score greater than 7 on the Young Mania Rating Scale (YMRS; Young *et al*., 1978); or meeting SCID-IV criteria for current depressive, manic or hypomanic episode ($n = 17$). Participants were excluded from participating in the control group for: lifetime history of Axis I disorder according to the SCID-IV ($n = 33$); subjective sleep complaints according to the Duke Structured Interview for Sleep Disorders (DSISD;

Edinger *et al.*, 2004; $n = 24$); and reported first-degree relatives with a diagnosis of BD or schizophrenia ($n = 6$). Participants were excluded from either group if they had a severe medical illness (e.g. autoimmune disorder, cancer; $n = 7$) or a confounding sleep disorder (e.g. sleep apnea, restless leg syndrome), based on their responses to the DSISD or based on Respiratory Distress Index (RDI) greater than 5 or Periodic Limb Movement (PLM) index greater than 15 found over the course of 1 night of polysomnography (PSG) screening in the lab ($n = 17$).

The demographics of the BD group ($n = 22$) and control group ($n = 22$) are presented in Table 1. There were no significant differences between the two groups. Participants ranged in age from 20 to 61 years, and represented a range of socioeconomic and ethnic groups. All participants in the BD group met diagnostic criteria for BD Type I ($n = 19$) or Type

Table 1 Demographics, sleep architecture variables, symptoms and impairment in the BD and control groups

	BD (n = *22*)	*Control* (n = *22*)	χ^2 *or* t
Demographics			
Age (in years)	33.95 (10.09)	39.95 (12.62)	1.74
Sex (% female)	90.9%	77.3%	-1.22
Marital status (% partnered)	31.8%	27.2%	-0.59
Education (% college graduate)	72.8%	72.7%	-0.20
Ethnicity (% white)	77.3%	59.1%	-1.17
Employed (%)	72.7%	90.9%	-1.55
Co-morbid diagnoses in BD group			
Panic disorder	4.5%	–	–
Agoraphobia	4.5%	–	–
Social phobia	9.1%	–	–
Specific phobia	27.3%	–	–
Obsessive compulsive disorder	11.5%	–	–
Post-traumatic stress disorder	4.5%	–	–
Generalized anxiety disorder	9.1%	–	–
Anorexia nervosa	4.5%	–	–
Binge eating disorder	4.5%	–	–
Illness history in BD group			
Age at illness onset (years)	18.57 (9.44)	–	–
Total past manic episodes	8.81 (7.60)	–	–
Total past depressive episodes	10.52 (10.04)	–	–
History of psychiatric hospitalization	76.2%	–	–
Time since last mood episode (months)	7.21 (11.54)	–	–
Mood symptoms at diagnostic visit and baseline sleep assessment			
YMRS diagnostic visit	3.19 (2.27)	1.80 (2.26)	-1.96
IDS-C diagnostic visit	7.35 (3.77)	5.20 (4.86)	-1.56
YMRS baseline sleep assessment	2.09 (2.20)	0.55 (1.06)	-2.97*
IDS-C baseline sleep assessment	5.55 (5.11)	2.36 (1.79)	-2.76*
Sleep architecture at baseline sleep assessment			
REM variables			
REM latency (min)	114.22 (48.42)	106.30 (54.66)	-0.51
REM%	22.42 (9.02)	22.49 (8.03)	0.03
Duration of the 1st REM period (min)	21.80 (17.53)	14.88 (11.10)	1.56
REM density	17.62 (12.29)	10.38 (8.20)	-2.30*
NREM variables			
Stage 1%	8.20 (6.99)	5.77 (4.46)	-1.37
Stage 2%	55.79 (16.10)	53.62 (8.67)	-0.55
SWS%	14.06 (10.71)	17.40 (9.46)	1.09
Symptoms and impairment at 3-month follow-up			
YMRS (mania)	3.57 (2.62)	1.00 (1.45)	-4.03***
IDS-C (depression)	11.65 (9.07)	2.09 (1.82)	-4.85***
WSAS (impairment)	13.67 (10.19)	4.41 (5.61)	-3.73**

Mean values are presented with standard deviations in parentheses.
BD, bipolar disorder; IDS-C, Clinician Rated Inventory of Depressive Symptomatology; NREM, non-rapid eye movement; REM, rapid eye movement; SWS, slow-wave sleep; WSAS, Work and Social Adjustment Scale; YMRS, Young Mania Rating Scale.
*$P \leq 0.05$; **$P \leq 0.005$; ***$P \leq 0.001$.

II ($n = 3$) according to the SCID-IV, and were determined to be inter-episode at the first visit based on SCID, IDS-C and YMRS criteria. Subsequently, the IDS-C and YMRS were used to determine that the participant was still inter-episode at all study visits preceding the follow-up. No participants in the control group were taking psychotropic or hypnotic medications. However, because the enrollment of a medication-free BD sample would be unfeasible and unrepresentative, BD participants were not asked to change or stop taking their prescribed medications. Thus, 21 of the 22 BD group participants were taking psychotropic medications. In addition, as BD is typically associated with the presence of co-morbid diagnoses (Kessler *et al*., 2005), participants were not excluded on the basis of co-morbid diagnoses other than current alcohol or substance abuse disorders. Detailed illness history for the BD group was assessed using the National Institute of Mental Health retrospective Life-Charting Methodology (NIMH-LCMr; Leverich and Post, 1993; one participant did not fully complete the NIMH-LCMr). Data on current co-morbidities and illness history in the BD group are presented in Table 1.

Procedures

Written informed consent was obtained, and the SCID-IV, DSISD, NIMH-LCMr, IDS-C, YMRS and demographics and medication questionnaires were administered at the diagnostic visit. An acclimation/screening night was then conducted as a control for first night effects and to screen for sleep disorders (e.g. sleep apnea).

The baseline sleep assessment was the second overnight visit, taking place approximately 1 month following the acclimation/screening night. Inter-episode status was assessed when participants arrived using the YMRS and IDS-C. PSG equipment was then attached. The timing of interviews and PSG set-up was carefully scheduled in order to allow participants to go to bed at their habitual preferred bedtime. A neutral mood induction was administered immediately prior to sleep to minimize the potential impact of transient pre-sleep affective states on sleep architecture. The neutral mood was induced using a well-validated procedure (Eich *et al*., 1994), which combined continuous music and autobiographical recall techniques. All participants reported being in a neutral mood prior to sleep, and there were no group differences in mood prior to ($t = -0.50$, $P > 0.60$) or following the mood induction ($t = 0.40$, $P > 0.60$).

The 3-month follow-up assessment took place an average of 82.0 days (SD = 51.4) after the baseline sleep assessment. It was conducted by phone and consisted of the YMRS, IDS-C and the Work and Social Adjustment Scale (WSAS; Mundt *et al*., 2002).

Measures

Polysomnography

Polysomnography involves the continuous and simultaneous recording of electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG). We used laboratory-based PSG (Compumedics USA Inc., Charlotte, NC, USA; Siesta802) that included four EEG leads (C3/A2, C4/A1, O1/A2, O2/A1), two EOG leads and two submental EMG leads. On the acclimation/screening night, respiratory airflow (using a nasal and oral thermistor), thoracic and abdominal displacement, finger pulse oximeter, electrocardiogram (two EKG leads), and a snoring sensor were added. Data were scored using the standard Rechtschaffen and Kales criteria for sleep staging (Rechtschaffen and Kales, 1968). REM latency corresponds to the time (in minutes) from sleep onset to the beginning of the first REM period of the night. REM density was calculated as the percentage of 5-s REM sleep periods that contained at least one eye movement (Werth *et al*., 1996).

For the BD group, an average total sleep time of 459.73 min (SD = 85.50) was available for scoring. This was marginally significantly longer than the average total sleep time of control participants, which was 409.52 min (SD = 73.28; $t = -2.02$, $P = 0.05$). Percentages of the various sleep stages were used instead of total minutes spent in each sleep stage due to group difference in total sleep time and because participants were not able to sleep past 09:00 hours because of resource limitations.

Mood symptom measures

The IDS-C (Rush *et al*., 1996) consists of 30 items, scored on a 0–3 metric, that assess depressive symptom severity for the preceding week. Scores less than 12 correspond to inter-episode status meaning no clinical depression is present. The YMRS (Young *et al*., 1978) consists of 11 items, scored on a 0–4 metric, that measure the severity of manic symptoms for the preceding week. Scores less than 8 correspond to inter-episode status meaning no clinical mania or hypomania is present. The IDS-C and the YMRS have good psychometric properties, and are widely used in medical and research settings (Rush *et al*., 1996; Young *et al*., 1978).

Functional impairment measure

The WSAS (Mundt *et al*., 2002) was used to assess mood-related functional impairment. This five-item measure has good internal consistency, test–retest reliability and sensitivity to disorder severity (Mundt *et al*., 2002). Individual items are rated on a 0–8 metric and assess the extent to which the participants' mood causes them to be impaired in occupational roles, home management, social leisure, private leisure and relationships.

Data analysis

Independent *t*-tests and chi-square tests were used to examine group differences in predictor and outcome variables. To address the effects of psychotropic medications on sleep architecture, we employed a multi-step patient-by-patient approach. ANOVAS were used to test the effect of participants' medication status on sleep architecture. Correlation analyses

were then used to test our *a priori* hypotheses. Continuous symptom and impairment measures were retained as the outcome measures of interest, as only a small subset of participants met criteria for hypomania or depression at follow-up. Where medications appeared to affect sleep architecture, secondary data analyses of our hypotheses were conducted in the medication subgroups.

RESULTS

As evident in Table 1, there were no group differences in symptoms at the diagnostic visit, but the BD group exhibited more depressive and manic symptoms than the control group at the baseline sleep assessment. At follow-up, the BD group had significantly more manic symptoms, depressive symptoms and functional impairment (based on WSAS total score and scores for each individual item) than the control group (Table 1). At follow-up, both manic (t = -2.66, $P < 0.05$) and depressive (t = -2.25, $P < 0.05$) symptoms in the BD group had increased since the baseline sleep assessment such that four participants (18.2%) met YMRS criteria for hypomania and 10 (45.5%) met IDS-C criteria for depression. With respect to sleep architecture, as evident in Table 1, the BD group had significantly greater REM density than the control group, though there were no other group differences.

To address medication effects, two of the authors (P. Eidelman and J. Gruber) independently classified each medication reported by participants as having no effect, an enhancing effect or a suppressing effect on REM, SWS and/or Stage 2 sleep, based on a detailed literature search. In cases where participants reported taking medications with conflicting sleep effects (e.g. Bupropion is a REM sleep enhancer and Fluoxetine is a REM sleep suppressor; Ott *et al*., 2004; Rush *et al*., 1998), we reasoned that these effects cancelled each other out. A list of potential medication effects on the sleep of each participant was generated by the two authors for 33% of participants, with a reliability of 100% for those coded by both authors. As reported in Table 2, ANOVAS and Tukey *post hoc* comparisons indicated that participants taking a medication that suppressed REM had a significantly longer latency to first REM than participants taking medications with no effect or an enhancing effect on REM. Participants taking a medication that suppressed REM also had greater REM density than participants taking a medication with no effect on REM. There were no other significant differences in sleep architecture based on medications (all $P > 0.10$; Table 2).

Table 3 presents correlations of baseline sleep architecture with baseline and 3-month follow-up symptoms and impairment. Sleep architecture was not significantly correlated with concurrent manic and depressive symptoms at the baseline sleep assessment in either participant group. However, in the BD group there were four significant correlations (out of 12) between baseline sleep architecture and follow-up symptoms. Duration of first REM and SWS% were positively correlated with manic symptoms, while REM density was positively correlated with depressive symptoms. Stage 2% was negatively correlated with manic symptoms. Additionally, there were three significant correlations (out of six) between sleep architecture and follow-up impairment in the BD group. REM density and SWS% were positively correlated with impairment, while Stage 2% was negatively correlated with impairment. In the control group, sleep architecture was not significantly correlated with follow-up symptoms. However, there was one significant correlation (out of six) for impairment, indicating that REM density was negatively correlated with impairment in the control group. Thus, seven significant correlations between baseline sleep architecture and follow-up symptoms and impairment emerged in the BD group, while only one significant correlation was found in the control group.

Correlations between sleep architecture and follow-up symptoms and impairment were repeated in subgroups of BD participants based on medication status to examine potential confounds of medication effects on REM latency and density. For REM latency all correlations remained

Table 2 Medication effects on sleep architecture in the BD group

Sleep architecture variables	*Medication effects* *No effect on REM* (n = *7*)	*Enhance REM* (n = *5*)	*Suppress REM* (n = *10*)	F
REM latency (min)	94.64 (20.86)	80.96 (45.36)	144.55 (48.27)	5.20*
REM%	23.57 (9.28)	20.95 (11.87)	22.36 (8.23)	0.11
Duration of 1st REM (min)	17.93 (12.55)	19.00 (18.10)	25.90 (20.78)	0.48
REM density	8.81 (5.99)	18.31 (13.83)	23.43 (12.06)	3.67*
	No effect on SWS (n = *10*)	*Enhance SWS* (n = *12*)	*Suppress SWS* (n = *0*)	
Stage 3%	7.27 (3.93)	9.06 (6.08)	–	0.64
Stage 4%	3.37 (3.03)	7.85 (8.36)	–	2.60
	No effect on Stage 2 (n = *14*)	*Enhance Stage 2* (n = *7*)	*Suppress Stage 2* (n = *1*)	
Stage 2%	54.62 (17.63)	56.54 (13.04)	65.80	0.23

Mean values are presented with standard deviations in parentheses.
REM, rapid eye movement; SWS, slow-wave sleep.
*$P \leq 0.05$.

Table 3 Correlations between sleep architecture at baseline sleep assessment and baseline and 3-month follow-up symptoms and impairment

Sleep variable	*Baseline YMRS (mania)* r	*Baseline IDS-C (depression)* r	*Follow-up YMRS (mania)* r	*Follow-up IDS-C (depression)* r	*Follow-up WSAS (impairment)* r
BD group (n = 22)					
REM variables					
REM latency	−0.06	−0.35	0.22	−0.12	0.04
REM%	−0.05	−0.09	0.16	0.23	0.20
Duration of 1st REM	−0.01	−0.32	0.48*	0.23	0.32
REM density	−0.11	−0.31	0.12	0.56**	0.54**
NREM variables					
Stage 2%	−0.13	−0.29	−0.47*	−0.15	−0.48*
SWS%	0.21	0.35	0.46*	0.23	0.47*
Control group (n = 22)					
REM variables					
REM latency	−0.12	−0.11	−0.39	−0.33	−0.19
REM%	0.23	−0.12	0.15	0.13	0.36
Duration of 1st REM	−0.18	−0.22	−0.01	−0.12	−0.22
REM density	−0.34	−0.32	−0.06	0.29	−0.46*
NREM variables					
Stage 2%	−0.16	0.15	0.28	−0.02	0.04
SWS%	−0.52	0.23	0.00	0.24	0.04
Secondary analyses in BD medication subgroups for REM density					
REM suppressing (n = 10)	–	–	0.11	0.72*	0.75*
No effect on REM (n = 7)	–	–	−0.33	−0.04	0.07

SWS%, sum of Stage 3% and Stage 4%; BD, bipolar disorder; IDS-C, Clinician Rated Inventory of Depressive Symptomatology; NREM, non-rapid eye movement; REM, rapid eye movement; SWS, slow-wave sleep; WSAS, Work and Social Adjustment Scale; YMRS, Young Mania Rating Scale.
*$P \leq 0.05$; **$P \leq 0.01$.

non-significant in both the BD subgroup taking medications that suppressed REM and the subgroup taking medications with no/enhancing effects on REM (all $P > 0.10$). However, as evident at the bottom of Table 3, while there were significant correlations between REM density and follow-up depressive symptoms and impairment in the BD subgroup taking medications that suppressed REM, these correlations were not significant in the subgroup taking medications with no effect on REM.

DISCUSSION

This study examined the cross-sectional and prospective associations of sleep architecture and symptoms and impairment in inter-episode BD. At the outset, we recognize that our discussion needs to be tempered due to the potential effects of medications on sleep in the BD group. Indeed, a primary aim of this study was to explore one strategy to manage the medication effects that need to be considered in neuropsychological and neurobiological research on BD, so we will return to this issue throughout the discussion that follows.

The first aim was to cross-sectionally examine the association between sleep architecture and symptoms and impairment in BD relative to non-psychiatric controls. We found no significant correlations between sleep architecture and concurrent symptoms at baseline in either group, although greater REM density was found in the BD group relative to the control group. These findings are in contrast to our hypotheses that REM and Stage 2 sleep would correlate with concurrent symptoms. One potential explanation may be our requirement that all participants be inter-episode. By definition, this restricts the range of depressive and manic symptoms in the sample, and decreases a likelihood of finding significant correlations (e.g. Guilford and Fruchter, 1978). A second potential explanation is that the neutral mood induction administered prior to sleep may have diffused pre-sleep mood and canceled out the effects inter-episode symptoms may have had on sleep architecture. However, the lack of significant group differences in mood prior to, and following, the neutral mood induction renders this account unlikely. Our finding of greater REM density in the BD group relative to controls is consistent with reports of increased REM activity in inter-episode BD (e.g. Knowles *et al.*, 1986) and in relatives of individuals with affective illness (e.g. Modell *et al.*, 2003), raising the possibility that increased REM density is a persistent sleep disturbance in BD. Given that we also found that participants who reported taking REM-suppressing medications demonstrated greater REM density, this group difference may also be attributable to medication effects. We will return to this possibility below.

The second study aim was to prospectively examine correlations between baseline sleep architecture and future

symptoms and impairment in BD. A number of significant findings emerged. Taking REM first, several significant correlations supported the hypothesis that increased REM activity would be associated with increased symptoms and impairment at follow-up in the BD group. Specifically, in the BD group longer duration of first REM was associated with more manic symptoms at the 3-month follow-up, while greater REM density was associated with more depressive symptoms and impairment at the 3-month follow-up. Thus, duration of first REM and REM density may have predictive value in inter-episode BD. The negative correlation between REM density and impairment in the control group, along with the findings that REM density is positively correlated with impairment and depression in the BD group, is consistent with the suggestion that REM serves a mood-regulatory role that is adaptive in non-psychiatric individuals but malfunctions in mood disorders (e.g. Knowles *et al*., 1986).

Several findings also supported the hypothesis that greater amounts of Stage 2 sleep would be associated with less follow-up symptoms and impairment in the BD group. Specifically, greater Stage 2% was associated with lower levels of manic symptoms and impairment in the BD group at follow-up. This is consistent with theories that Stage 2 sleep fulfills an important restorative function (Hayashi *et al*., 2005). Although Stage 2 sleep has received comparatively little attention in mood disorder research to date, our findings raise the possibility that Stage 2 sleep may have some protective value. Studies demonstrating positive associations between treatment response and increased Stage 2 sleep in BD (e.g. Hinze-Selch *et al*., 1997) are also suggestive of the importance of Stage 2 sleep.

Given the mixed findings in the literature to date, we did not make specific hypotheses regarding SWS, including it in our analyses on an exploratory basis. Results indicated that greater SWS% predicted more manic symptoms and impairment in the BD group at the 3-month follow-up. This was somewhat surprising, given that past research has suggested that increased levels of SWS appear necessary to normalize depressed mood (e.g. Borbely, 1982; Jovanovic, 1977). There are several possible explanations for our findings. First, in consideration with findings that greater Stage 2% was associated with less manic symptoms and impairment at the follow-up, it is important to note that the durations of Stage 2 sleep and SWS may change in proportion to each other. Indeed, while it appears that disturbances in REM and non-rapid eye movement (NREM) sleep are not reciprocal (Armitage, 2007), changes in the different stages of NREM sleep are likely to impact other NREM sleep stages. Second, perhaps even prior to the baseline assessment, the participants who later developed manic symptoms were starting to increase their physical activity. Even a slight increase in exercise and physical activity is known to increase SWS (Naylor *et al*., 2000). Third, participants who later developed manic symptoms may have already been displaying reduced sleep need prior to the baseline sleep assessment and were, therefore, becoming sleep deprived. Based on the two-process model of sleep regulation and sleep deprivation studies, increased wakefulness is associated with greater SWS over the course of the night (e.g. Borbely, 1982; Brunner *et al*., 1993). Fourth, perhaps there are bi-directional effects. Specifically, perhaps greater SWS may be detrimental in BD, overcompensating for the need to regularize depressed mood and inducing a shift to the opposite end of the mood spectrum toward manic symptoms.

Our third aim was to address the role of psychotropic medications. To address potentially confounding effects of medications in our analyses, we employed a multi-step approach based on a detailed patient-by-patient literature review of medication sleep architecture effects. By applying this approach, in lieu of requesting that all participants be medication free prior to participating, we reasoned that we would be able to recruit a participant sample that is more representative of the larger population of adults with BD. In the present study, the main concern was the association of REM-suppressing medications with greater REM density. It is possible that this medication effect confounded correlations between REM density and symptoms and impairment at 3 months in the BD group. If this is the case, this medication-related finding raises a number of possibilities. First, BD individuals who are prone to depression may also be more likely to respond to REM-suppressing medications. Second, REM-suppressing medications may render individuals more susceptible to depression and impairment, although this seems unlikely as neither follow-up depressive symptoms (t = -1.74, $P > 0.10$) nor impairment (t = -1.70, $P > 0.10$) were greater in participants taking REM-suppressing medications than in participants taking medications with no REM effects. Third, REM-suppressing medications may affect the mood-regulatory function of REM, thereby intensifying the association of REM density with future depression and impairment. Thus, further research on REM sleep in BD is needed to clarify the relationship between medication effects, REM density and depressive symptoms.

There were several key lessons learned from our approach to medications that should be addressed in future studies of BD. First, we recognize that some of the medication subgroups were small (e.g. only one participant was taking a medication that suppresses Stage 2 sleep). Thus, some statistical tests were underpowered to detect meaningful group differences in sleep architecture based on medication regimen. Future studies with larger samples could address medication confounds by utilizing medication subgroups as covariates in statistical analyses. Second, medication usage should be assessed at follow-up to check if a medication change or discontinuation may have occurred, potentially influencing the associations observed between sleep architecture and follow-up symptoms and impairment. Third, we reasoned that sleep architecture effects of medications that enhanced and suppressed the same sleep stage would cancel out. Although this decision makes sense at one level, medication interaction studies have not yet been conducted to assess the validity of this assumption. Fourth, investigators had to be aware that medications may be prescribed to participants on the basis of underlying factors,

such as a tendency to exhibit particular symptom clusters (e.g. Swann *et al*., 2002). These underlying factors may affect both sleep architecture and the participant's medication regimen. In order to assess this possibility, it may be useful to obtain a more detailed illness history or obtain permission to contact the prescribing physician in order to discuss the physician's reasons for prescribing the medications taken by participants. Finally, the effects of medications on sleep architecture are undoubtedly quite complex, and include effects other than increasing and decreasing sleep stages. For example, benzodiazepine receptor agonists may increase EEG beta activity while decreasing delta and theta activity (Bastien *et al*., 2003). While we recognize the limitations of our approach to medications, we aimed to begin a process of developing a method for dealing with pharmacological treatments that would allow for the study of a diverse and representative sample of individuals diagnosed with BD. We hope that future investigations will further elaborate on our approach, utilizing lessons learned about the issues discussed above.

Several limitations need to be considered. First, the sample size was relatively small and largely composed of female participants. Replication in larger and more diverse samples is warranted. Second, we did not correct for multiple comparisons. While this increases the risk of Type I error, given that this is a relatively new research area, we were also concerned about decreasing the risk of Type II error (Nakagawa, 2004) so as to maximize information gleaned from this initial study. The small number of significant correlations in the control group is noteworthy. On the basis of chance, if the results reflected false positives, more significant findings had to have emerged in the control group. Third, we acknowledge that the stages of NREM sleep assessed are not entirely independent, and that we cannot ascertain causal relationships between sleep stages and subsequent symptoms and impairment. Fourth, we utilized one night of PSG as our assessment of sleep architecture. Future studies should assess sleep architecture over multiple nights. Finally, the impact of co-morbid diagnoses should be considered. In future studies, it may be useful to include a comparison group with a diagnostic profile similar to the co-morbid diagnoses in the BD group in order to ascertain the impact of co-morbid disorders on sleep architecture.

Overall, our results point to sleep architecture as a potential illness-maintaining mechanism in BD. Supporting the hypothesis that the mood-regulatory role of REM may malfunction in mood disorders, REM activity was positively correlated with a future increase in symptoms and impairment in our sample. With respect to NREM sleep, we found that SWS activity was also positively correlated with increased symptoms and impairment. In contrast, our results suggest that Stage 2 sleep may play a protective role in BD, as it was correlated with decreased symptoms and impairment at follow-up. Indeed, it may be the case that the ways in which REM and NREM function in BD may be altered even in the inter-episode period, such that sleep architecture characteristics are predictive of future symptoms and impairment. Furthermore, by taking a new approach to medication effects, we were able to assess sleep in an inter-episode, representative, medicated BD sample to demonstrate that medications do not have to be inherent and intractable confounding factors in research of severe psychopathology.

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DISCLOSURE

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REFERENCES

Armitage, R. Sleep and circadian rhythms in mood disorders. *Acta Psychiatrica Scandinavica*, 2007, 115: 104–115.

Bastien, C. H., LeBlanc, M., Carrier, J. and Morin, C. M. Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. *Sleep*, 2003, 26: 313–317.

Benca, R. M., Obermeyer, W. H., Thisted, R. A. and Gillin, C. Sleep and psychiatric disorders: a meta-analysis. *Arch. Gen. Psychiatry*, 1992, 49: 651–668.

Borbely, A. A. A two process model of sleep regulation. *Hum. Neurobiol*., 1982, 1: 195–204.

Borbely, A. A. The S-deficiency hypothesis of depression and the two-process model of sleep regulation. *Pharmacopsychiatry*, 1987, 20: 23–29.

Brunner, D. P., Dijk, D. J. and Borbely, A. A. Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep*, 1993, 16: 100–113.

Cartwright, R., Young, M. A., Mercer, P. and Bears, M. Role of REM sleep and dream variables in the prediction of remission from depression. *Psychiatry Res*., 1998, 80: 249–255.

De Gennaro, L. and Ferrara, M. Sleep spindles, an overview. *Sleep Med. Rev*., 2003, 7: 423–440.

de Maertelaer, V., Hoffman, G., Lemaire, M. and Mendlewicz, J. Sleep spindle activity changes in patients with affective disorders. *Sleep*, 1987, 10: 443–451.

Edinger, J. D., Bonnet, M. H., Bootzin, R. R. *et al*. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine work group. *Sleep*, 2004, 27: 1567–1596.

Eich, E., Macaulay, D. and Ryan, L. Mood dependent memory for events of the personal past. *J. Exp. Psychol. Gen*., 1994, 123: 201–215.

Feinberg, I., Maloney, T. and Campbell, I. G. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. *J. Psychiatr. Res*., 2000, 34: 423–438.

First, M. B., Spitzer, R. L., Gibbon, M. and Williams, J. B. W. *Structured Clinical Interview for DSM-IV – Patient Version*. Biometrics Research Department, New York State Psychiatric Institute, New York, 1994.

Ghaemi, S. N., Hsu, D. J., Thase, M. E. *et al*. Pharmacological treatment patterns at study entry of the first 500 STEP-BD participants. *Psychiatr. Serv*., 2006, 57: 660–665.

Giles, D. E., Rush, A. J. and Roffwarg, H. P. Sleep parameters in bipolar I, bipolar II, and unipolar depressions. *Biol. Psychiatry*, 1986, 21: 1340–1343.

Giles, D. E., Kupfer, D. J., Rush, J. A. and Roffwarg, H. P. Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. *Am. J. Psychiatry*, 1998, 155: 192–199.

Guilford, J. P. and Fruchter, B. *Fundamental Statistics in Psychology and Education*, 6th edn. McGraw-Hill, New York, 1978.

Harvey, A. G. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony and regulation. *Am. J. Psychiatry*, 2008, 165: 820–828.

Hayashi, M., Motoyoshi, N. and Hori, T. Recuperative power of a short daytime nap with and without stage 2 sleep. *Sleep*, 2005, 28: 829–836.

Hinze-Selch, D., Mullington, J., Orth, A. *et al*. Effects of clonazepine on sleep: a longitudinal study. *Biol. Psychiatry*, 1997, 42: 260–266.

Hudson, J. I., Lipinski, J. F., Frankenburg, F. R., Grochocinski, V. J. and Kupfer, D. J. Electroencephalographic sleep in mania. *Arch. Gen. Psychiatry*, 1988, 45: 267–273.

Hudson, J. I., Lipinski, J. F., Keck, P. E., Jr *et al*. Polysomnographic characteristics of young manic patients: comparison with unipolar depressed patients and normal control subjects. *Arch. Gen. Psychiatry*, 1992, 49: 378–383.

Jackson, A., Cavanagh, J. and Scott, J. A systematic review of manic and depressive prodromes. *J. Affect. Disord.*, 2003, 74: 209–217.

Jernajczyk, W. Latency of eye movement and other REM sleep parameters in bipolar depression. *Biol. Psychiatry*, 1986, 21: 465–472.

Jovanovic, U. J. The sleep profile in manic-depressive patients in the depressive phase. *Waking Sleeping*, 1977, 1: 199–210.

Judd, L. L., Akiskal, H. S., Schettler, P. J. *et al*. The long-term natural history of weekly symptomatic status of bipolar I disorder. *Arch. Gen. Psychiatry*, 2002, 59: 530–537.

Kessler, R. C., Chiu, W. T., Demler, O. and Walters, E. E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry*, 2005, 62: 617–627.

Knowles, J. B., Cairns, J., MacLean, A. W. *et al*. The sleep of remitted bipolar depressives: comparison with sex and age-matched controls. *Can. J. Psychiatry*, 1986, 31: 295–298.

Leverich, G. S. and Post, R. M. *The NIMH Life Chart Manual for Recurrent Affective Illness: The LCMS-S (Self Version)*. NIMH Monograph, Biological Psychiatry Branch, Bethesda, MD, 1993.

Mendelson, W. B., Sack, D. A., James, S. P. *et al*. Frequency analysis of sleep EEG in depression. *Psychiatry Res.*, 1987, 21: 89–94.

Modell, S., Huber, J., Holsboer, F. and Lauer, C. J. The Munich vulnerability study on affective disorders: risk factors for unipolarity versus bipolarity. *J. Affect. Disord.*, 2003, 74: 173–184.

Modell, S., Ising, M., Holsboer, F. and Lauer, C. J. The Munich vulnerability study on affective disorders: premorbid polysomnographic profile of affected high risk probands. *Biol. Psychiatry*, 2007, 58: 694–699.

Mundt, J. C., Marks, I. M., Shear, M. K. and Greist, J. M. The work and social adjustment scale: a simple measure of impairment in functioning. *Br. J. Psychiatry*, 2002, 180: 461–464.

Nakagawa, S. A farewell to Bonferroni: the problems of low statistical power and publication bias. *Behav. Ecol.*, 2004, 15: 1044–1045.

Naylor, E., Penev, P. D., Orbeta, L. *et al*. Daily social and physical activity increases slow-wave sleep and daytime neuropsychological performance in the elderly. *Sleep*, 2000, 23: 87–95.

Ott, G. E., Rao, U., Lin, K., Gertsik, L. and Poland, R. Effect of treatment with bupropion on EEG sleep: relationship to antidepressant response. *Int. J. Neuropsychopharmacol.*, 2004, 7: 275–281.

Perlman, C. A., Johnson, S. L. and Mellman, T. A. The prospective impact of sleep duration on depression and mania. *Bipolar Disord.*, 2006, 8: 271–274.

Rao, U., Dahl, R. E., Ryan, N. D. *et al*. Heterogeneity in EEG sleep findings in adolescent depression: unipolar versus bipolar clinical course. *J. Affect. Disord.*, 2002, 70: 273–280.

Rechtschaffen, A. and Kales, A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. US Department of Health Education and Welfare, Bethesda, MD, 1968.

Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B. and Trivedi, M. H. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol. Med.*, 1996, 26: 477–486.

Rush, A. J., Armitage, R., Gillin, J. C. *et al*. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorders. *Biol. Psychiatry*, 1998, 44: 3–14.

Sitaram, N., Nurenberger, J. I., Gershon, E. S. and Gillin, J. C. Cholinergic regulation of mood and REM sleep: potential model and marker of vulnerability of affective disorder. *Am. J. Psychiatry*, 1982, 139: 571–575.

Swann, A. C., Bowden, C. L., Calabrese, J. R., Dilsaver, S. C. and Morris, D. D. Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. *Neuropsychopharmacology*, 2002, 26: 530–536.

Wehr, T. A., Sack, D. A. and Rosenthal, N. E. Sleep reduction as a final common pathway in the genesis of mania. *Am. J. Psychiatry*, 1987, 144: 210–214.

Werth, E., Dijk, D. J., Achermann, P. and Borbely, A. A. Dynamics of the sleep EEG after an early evening nap: experimental data and simulations. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 1996, 271: R501–R510.

Young, R. C., Biggs, J. T., Ziegler, V. E. and Meyer, D. A. A rating scale for mania: reliability, validity and sensitivity. *Br. J. Psychiatry*, 1978, 133: 429–443.