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A Preliminary Study of Central Nervous System Arousal and Sleep Quality in Bipolar Disorder

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Abstract
Sleep disturbances are commonly reported in patients with bipolar I disorder (BPI) and are risk factors for mood episodes. In other populations, central nervous system (CNS) hyperarousal is associated with sleep initiation and maintenance problems, and CNS hypoarousal is associated with increased sleep drive. However, it is unclear whether CNS arousal levels are a useful index of sleep disruption in BPI. This study aimed to investigate daytime CNS arousal levels in relation to perceived sleep quality in BPI. Resting EEG, mood state, and self-reported sleep quality data were collected from 34 individuals with BPI. CNS hyperarousal was associated with pervasive poor subjective sleep quality including increased sleep disturbances, increased sleep latency, and reduced global sleep quality. CNS hypoarousal was associated with greater daytime sleepiness, indicating reduced arousal. These preliminary findings suggest that CNS arousal may be a useful index for identifying individuals at high risk for relapse into a mood episode. A limitation of this study is the use of self-report instruments for sleep quality assessment. Future research should investigate the temporal relationship of CNS arousal to sleep disturbances using objective measurements of sleep quality such as polysomnography. If these findings are replicated, measures of CNS arousals may allow for identification of high-risk patients with BPI.

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Bipolar I disorder (BPI) affects approximately 3% of the general population [1]. Although recent advancements in pharmacological treatments have proven effective for reducing the symptoms associated with BPI, many continue to experience significant functional impairment, and the risk of relapse is great [2]. Research to improve the identification prodromal individuals at increased risk for relapse is urgently needed.

Sleep disturbance is the most common prodromal symptom of mania and the sixth most common prodromal symptom of depression [3]. Further research has linked insomnia to the onset of manic episodes [3]. BPI manic episodes are characterized by sleep disturbances including "decreased need for sleep," while depressive episodes are characterized by "changes in sleep" and "fatigue or loss of energy" [4]. Accordingly, recent research has focused on sleep-specific interventions to reduce the risk of relapse in people with BPI [5]. A modified form of cognitive behavioral therapy for insomnia has been shown to be effective for reducing the hypomania/mania relapse rate, reducing the number of days in a bipolar episode, and early data suggest it may even lower the overall mood episode relapse rate [5].

Central nervous system (CNS) arousal is a construct, quantified using resting EEG, that has received substantial attention in other populations as a biological correlate of sleep disturbance [6–9]. The NIMH RDoC project has identified arousal as one of the 7 pillars believed to be important for investigating psychiatric disorders [10]. The literature on insomnia has identified CNS hyperarousal, characterized by elevated high frequency (i.e., beta and gamma) resting EEG power during both eyes open and eyes closed conditions, as a biological correlate of sleep disruption [11–16] and arousal [17, 18]. Loo further suggested that frontal beta activity was a more precise measure of arousal than global beta activity [17]. Freedman and Sattler [12] were among the first to publish data suggesting that sleep onset difficulties in people with insomnia is associated with CNS hyperarousal at sleep onset. In 1992, Merica and Gaillard [19] published findings that supported and extended the work by Freedman and Sattler [12] by suggesting that CNS hyperarousal, operationalized as elevated high frequency resting EEG power, is not just isolated to periods of wakefulness, but also persists into sleep in people with insomnia. Further studies have also suggested an effect of arousal on EEG activity [18]. Based on these findings, Jacobs, Benson, and Friedman [9] developed an intervention that reduced the presleep CNS hyperarousal (i.e., elevated frontal beta EEG power) in people with insomnia, and this reduction was associated with improved sleep quality. Taken together, CNS hyperarousal may be associated with sleep initiation and maintenance difficulties, and such an index may be useful in identifying individuals with BPI at increased risk for sleep disturbance.

In contrast, CNS hypoarousal may be an index of sleep drive and reduced arousal. Cajochen et al. [6] reported that fatigue ratings were associated with increased low frequency EEG power, and these oscillations increased with sleep deprivation. As such, increased low frequency daytime resting EEG power may be a useful index of sleep drive. Relatedly, Heller [8] reviewed a number of studies that suggest reduced brain activity (i.e., increased alpha power) in the right parietotemporal region to be associated with reduced emotional arousal, and may be a useful index of emotional arousal. While CNS hyperarousal may be associated with increased alertness and difficulties falling asleep, CNS hypoarousal may be associated with reduced alertness and an increased sleep drive [16].

Although a large body of knowledge has been accumulated regarding the neuronal correlates of sleep disturbance in insomnia, relatively little is known about these correlates in individuals with BPI. Several studies investigating differences in resting EEG power between participants with BPI and controls have reported decreased alpha and increased delta and theta power among participants with BPI [20]. The association of daytime CNS hyperarousal and sleep quality in depressed patients has been investigated [21]. Further, daytime CNS arousal in bipolar disorder has recently received attention as a possible indicator of depressed and manic states [22, 23]. However, no study to date has investigated the relationship between daytime resting EEG and perceived sleep quality in individuals with BPI. Identification of indices of sleep disturbance may allow for the early detection of patients with BPI who are at high risk for sleep disturbance and, therefore, at high risk for the onset of a mood episode. The goal of the present study was to investigate the utility of CNS arousal indices as a measure of sleep quality in people with BPI.

This study hypothesized that among euthymic patients with BPI: (I) CNS hyperarousal would be associated with poorer self-reported global sleep quality, more sleep disturbances, reduced sleep efficiency, and increased sleep onset latency; (II) CNS hypoarousal would be associated with increased self-reported sleepiness and decreased arousal; and, (III) given the limited previous research, an exploratory test of the influence of medication on the relationship between sleep disturbances and CNS arousal was conducted.

Method

Participants

Patients with bipolar disorder with no personal or family history of mood or psychotic disorder were recruited to the Prechter Longitudinal Study of BD at the University of Michigan between 2005 and 2010 [24]. All participants were under the care of psychiatrists involved in the longitudinal study. This study was approved by the UM IRB. Diagnostic interviews were completed with the Diagnostic Interview for Genetic Studies [25], and clinicians rated mood with the Hamilton Depression Rating Scale [26] and the Young Mania Rating Scale [27]. Exclusion criteria for the longitudinal study included: (1) age <18, (2) neurological disorders, a Hamilton Depression Rating Scale score greater than 8, and (3) intellectual disability (WAIS IQ <70). Participants enrolled in the longitudinal study, without a history of substance abuse or head injury, and who indicated interest in future research studies were contacted. Participants who met study criteria were contacted by telephone and informed of the nature, costs, and benefits of the study. A total of 40 euthymic participants with BPI completed EEG recording. Six participants were excluded (3 for excessive EEG artifacts and 3 for incomplete Pittsburgh Sleep Quality Index [PSQI] surveys). The analyses presented in this paper include 34 participants with BPI (See Tables 1, 2 and 3 for demographics, medication status, and comorbidities, respectively).

Measures

Current mood state was assessed using the Beck Depression Inventory-II [28] and the Altman Self-Report Mania Scale [29]. The PSQI [30] was used to assess the participants' sleep quality over the past month and was acquired during the participants' regularly scheduled checkups for the longitudinal study during the month of EEG recording. The PSQI has been shown to be a highly reliable and valid instrument for differentiating good-sleepers from poor-sleepers and is generally considered a "gold standard" self-report instrument to quantify sleep disturbance [30]. Subscales utilized included sleep latency (time in bed prior to sleep onset), sleep efficiency (time asleep/time in bed × 100; calculated using raw scores to maximize variance), sleep disturbance (frequency of sleep disturbances), and daytime sleepiness. A global PSQI score was also calculated as a composite score across subscales.

Procedure

Prior to their visit, participants were asked to wear comfortable clothing, refrain from alcohol, and limit their caffeine intake to one drink on the selected day. Participants were compensated USD 20 per hour for their time. The timing of the scheduled EEG recording varied from mid-morning to mid-afternoon. Informed consent was obtained following the guidelines of the Institutional Review Board of the University of Michigan (HUM00041294).

The study procedure included a structured mood assessment, resting EEG recording, and several self-report questionnaires and computerized neuropsychological tasks that are not discussed here because they are not relevant to the study. The order of the conditions was counterbalanced across the participants. The resting EEG session consisted of a 3-min eyes-open condition, where participants were instructed to fixate their eyes on a small black cross on a white background, and an eyes-closed condition, where participants were informed to close their eyes and try not to fall asleep until they hear a beep signifying the end.

Table 1. Descriptive statistics (n = 34)

	Mean	SD
Age, years, range (24–60)	42.0	10.7
Beck Depression Inventory	10.4	7.8
Altman	4.2	3.6
Global PSQI	7.7	3.1
Mania episodes, *n*	20.5	10.1
Depression episodes, *n*	36.4	20.1
Hypomania episodes, *n*	47.0	22.1
Mixed episodes, *n*	2.4	1.8
Affective Psychosis episodes, *n*	2.5	2.0
Hx of Suicidal ideation, %	97.14	
Age onset	5.3	15.8
1st degree relative with BP	3.8	6.8
2nd degree relative with BP	0.2	0.5

Data Acquisition

EEG data were recorded in a temperature controlled, electrically shielded room with 32 Ag/AgCl electrodes placed in a Lycra stretchable cap per the International 10/20-System with FCz as a common ground reference. Vertical electro-oculogram data were recorded from 2 channels placed beneath the left eye and at Fp1. EEG and electro-oculogram signals were amplified 500 times by BrainCap MR-32 system (BrainProducts, GmbH, Munich, Germany) and digitally sampled at 5,000 Hz. Impedance for all electrodes was kept below 5 kΩ.

Data Analysis

Using BrainVision Analyzer (BrainProducts, GmbH, Munich, Germany), EEG data were down-sampled offline at 512 Hz, re-referenced to average mastoids ([TP9 + TP10]/2). Then, EMG artifacts were manually removed from the data. High-pass filtering at 0.5 Hz was used to attenuate low frequency oscillations and signal drift. Eye movements were removed using ICA [20]. One second segments of EEG data were extracted through a Hamming window to reduce spurious estimates of spectral power, and adjacent segments were overlapped by 0.5 s to minimize the loss of data due to Hamming window extraction. For each resultant segment, Fast Fourier Transform was used to derive estimates of absolute spectral power (μV^2) per 1-Hz frequency bin. Power values were converted to power density values (μV^2/Hz) for the EEG frequency bands proposed by this study (theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–30 Hz, gamma: 30–80 Hz). The spectral power density values were averaged across all segments within a frequency band and normalized via natural log-transformation. The resultant normalized and artifact-corrected power density values were averaged across the scalp (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) to provide a summary power density value for each frequency band. Based on Heller's [8] work, alpha power at right relative to left posterior electrodes was used (P3–P4) to estimate CNS hypoarousal. Based on prior research, global beta activity during the eyes-open and eyes-closed condition was used to estimate CNS hyperarousal [15]. Further, based on the work of Loo et al. [17], frontal beta activity during the eyes-open and eyes-closed conditions was used to estimate CNS hyperarousal.

The data were analyzed using the Statistical Package for Social Sciences. The seven subscales and a global score were calculated from the PSQI for each participant. For continuous PSQI variables (sleep efficiency and global PSQI score) that demonstrated a normal distribution, Pearson's *r* was calculated to test the association between self-reported sleep quality and measures of CNS arousal. For ordinal PSQI variables (sleep latency, sleep disturbance, and daytime sleepiness), Spearman's *rho* was used.

To examine the influence of prescription medications on the EEG variables, the medications of each participant were recorded and categorized into the following categories: lithium, antipsychotics, antiepileptics, antidepressants, benzodiazepines, and hypnotics (Table 2). Preliminary correlations testing the association of medication usage to EEG frequency bands were run prior to conducting the main analyses to determine any preliminary effects of medication usage on the EEG. For the EEG frequency bands that were significantly influenced by medications, follow-up analyses were conducted to assess any moderating effects. To address the lack of power in the regression model due to low sample size, follow-up Fisher's Z tests were used to compute Z values for each correlation between the sleep variable and the CNS arousal variable, and the significance of the Z score differences was used to test whether the medication status significantly moderated the results.

Table 2. Medication data

	Percentages
0 medication	15.2
1 medication	21.2
>1 medication	60.6
Benzodiazapines (10/3% PRN)	17.2
Lithium	33.3
Mood stabilizer	48.5
Antipsychotic	30.3
Antidepressant	60.6
Neurontin	3.0
Gender (F/M)	20/14

Table 3. Comorbidity data

	Percentages
Any comorbidity	77.10
SUD	68.60
Anxiety disorders	31.40
ADHD	11.40
Psychosis	62.50

SUD, Substance Use Disorders; ADHD, Attention Deficit Hyperactivity Disorder.

Results

CNS Hyperarousal and Sleep Disruption

Elevated beta activity during the eyes-open condition was associated with a greater frequency of self-reported sleep disturbances ($rho[34] = 0.44$, $p < 0.01$). Elevated gamma activity during the eyes-open condition was similarly associated with a greater frequency of self-reported sleep disturbances ($rho[34] = 0.37$, $p = 0.02$). Elevated beta activity during the eyes-open condition was associated with poorer global sleep quality ($rho[34] = 0.33$, $p = 0.03$). Elevated gamma activity during the eyes-open condition was similarly associated with poorer global sleep quality ($rho[34] = 0.34$, $p = 0.03$). Elevated beta activity across the scalp during the eyes-closed condition was only marginally associated with increased sleep latency ($rho[34] = 0.25$, $p = 0.07$). However, the average beta activity over the frontal sites (F3, Fz, F4) was significantly associated with increased sleep latency ($rho[34] = 0.34$, $p = 0.03$). See Table 4 for a summary of these correlation analyses. Taken together, CNS hyperarousal was associated with a greater frequency of self-reported sleep disturbances, increased sleep latency, and poorer global sleep quality. CNS hyperarousal, however, was not significantly associated with alterations in sleep efficiency.

CNS Hypoarousal and Daytime Sleepiness

Greater rightward asymmetries in posterior alpha power during the eyes-closed condition was associated with increased daytime sleepiness ($rho[34] = -0.41$, $p \leq 0.01$). However, contrary to the hypothesis of *increased* theta power, daytime sleepiness was associated with *reduced* resting theta power during the eyes-open condition ($rho[34] = -0.44$, $p = 0.01$).

Effects of Medication Usage on CNS Arousal Measures

Preliminary analyses demonstrated a significant effect of antipsychotic, antidepressant, and antiepileptic usage on CNS hyperarousal. Antipsychotics were associated with reduced eyes-closed beta activity ($\beta = -0.29$, $F[1, 26] = 4.38$, $p = 0.05$, $\eta^2 = 0.14$), antidepressants were associated with increased eyes-closed beta activity ($\beta = 0.34$, $F[1, 26] = 6.81$, $p = 0.02$, $\eta^2 = 0.21$), and antiepileptics were associated with reduced eyes-open gamma activity ($\beta = -0.25$, $F[1, 26] = 4.24$, $p = 0.05$, $\eta^2 = 0.14$). However, when entered into a regression, these medications did not significantly moderate the relationship between sleep quality and CNS hyperarousal or CNS hypoarousal. To address the lack of power in the regression model due to low sample size, follow-up Fisher's Z tests were computed to ensure these effects were not moderated by medication status. The relationship of

Table 4. Correlations

Variable 1	Variable 2	rho	*p* value	Power
Beta EO	Sleep disturbance	0.44	<0.01	0.82
Gamma EO	Sleep disturbance	0.37	0.02	0.66
Beta EO	Global sleep quality	0.33	0.03	0.55
Gamma EO	Global sleep quality	0.34	0.03	0.58
Beta EC	Sleep latency	0.25	0.07	0.34
Frontal beta EC	Sleep latency	0.34	0.03	0.58
Alpha asymmetry EC	Daytime sleepiness	–0.41	<0.01	0.76
Theta EO	Daytime sleepiness	–0.44	0.01	0.82

beta activity during the eyes-open condition to self-reported sleep disturbances was not significantly moderated by antipsychotic or antidepressant usage (Z = –0.42, $p = 0.67$). Further, the relationship of beta activity during the eyes-open condition to global sleep quality was not significantly moderated by antipsychotic (Z = –1.31, $p = 0.19$) or antidepressant usage (Z = –1.24, $p = 0.22$).

Discussion

The findings from this study suggest that changes in self-reported sleep quality in euthymic individuals with BPI can be detected via alterations in resting EEG patterns. The CNS hyperarousal hypothesis of insomnia posits that high frequency power during wakefulness persists into sleep and is associated with poorer sleep quality and disrupted sleep processes [19]. Accordingly, this study found that CNS hyperarousal is associated with poorer perceived global sleep quality in BPI and is specifically linked to increased perceived sleep disturbances and sleep onset latency. CNS hyperarousal's association with symptoms of mind racing may lead people with BPI to have difficulty quieting their mind to sleep [14]. CNS hyperarousal may be a useful indicator of those at high risk for initiating and maintaining sleep, which would elevate their risk for the onset of a (hypo) manic episode.

In this sample, rightward asymmetries in alpha power are associated with increased daytime sleepiness. In accordance with data from Heller [8], linking alpha power in the right parietotemporal region with CNS arousal, increased rightward parietal asymmetry in alpha power is associated with reduced CNS arousal as indicated by increased self-reported daytime sleepiness. CNS hypoarousal may be useful in identifying individuals with BPI exhibiting signs of daytime sleepiness.

As expected, resting theta power is associated with altered sleepiness and motivation, which may reflect CNS arousal. However, the effect of this association was unexpected. Reduced resting theta power was associated with increased daytime sleepiness in people with BPI. Based on findings from a study in a healthy control sample suggesting that theta power is associated with sleep drive during sustained wakefulness [6], it was expected that increased, not reduced, theta power would be associated with increased daytime sleepiness. It is possible that other unexplained variables may impact the relationship between CNS hypoarousal and daytime sleepiness in people with BPI. A possible explanation of this unexpected result is that increased theta may reflect a deficient build-up of sleep pressure during the day possibly due to excessive time in bed, which may indicate sleep pathology in the participants [6].

This study has several limitations. The participants in this study were recruited from a larger longitudinal study of bipolar disorder to capitalize on the unique opportunity to study a group that is typically difficult to recruit. The longitudinal study restricted recruitment to people residing in Southeastern Michigan, and, consequently, participants are more likely to be Caucasian and have a higher level of education. Further, participants are likely to be of higher functioning than typical patients with BPI because of the level of executive functioning necessary to keep up with the demands associated with the longitudinal study. A lack of adjustment for multiple comparisons due to the sample size of the study is a notable limitation, which could result in Type I error. This study included people of varying medication statuses, and these medications may have influenced our findings. To control for substance use effects, participants were asked to limit coffee use to one drink on the day of the study; however, a limitation of this study may be that heavy coffee drinkers who were asked

to reduce their caffeine intake may have demonstrated altered arousal states due to withdrawal. Although a newer method that is validated for assessing CNS arousal during EEG recordings has been developed [31, 32], due to the low sample size in this study, we were unable to utilize this method.

This study found a link between medication usage and measures of CNS arousal: antipsychotic and antidepressant usage was a moderator of beta activity, and antiepileptic usage was a moderator of gamma activity. Notably, the associations between self-reported sleep quality and CNS arousal tested in this study were not significantly moderated by these medications. Another limitation is that polysomnography was not used to assess sleep quality. The low sample size prevented us from using multivariate statistics as an analytic strategy, introducing the possibility of inflated alphas. Although polysomnography is the "gold standard" to measure sleep quality, it is very costly and time intensive for both the participants and the researchers. Nevertheless, this study supports the notion that this type of further study is warranted.

Maintaining adequate sleep quality and minimizing sleep disturbances can reduce the risk of relapse and severity of mood episodes. Empirically supported treatments that address sleep quality in BPI have demonstrated considerable promise in reducing the number and severity of mood episodes [5]. Research focused on identifying individuals at high risk for sleep disturbances, and specific mechanisms related to sleep quality may allow for future development of an early detection and intervention program to attenuate the risk of the onset of a mood episode. This study demonstrated that CNS hyperarousal and CNS hypoarousal may be useful indices for identifying individuals with BPI at high risk for sleep disturbance and, thus, relapse. Future research should examine the intraindividual variability in CNS hyper/hypo-arousal and their temporal relationship to sleep disturbances in BPI.

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