

Sleep, Depression, and Resilience: *Connecting the sleeping and waking brain*

by

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Dedication

In the memory and spirit of Dr. Christopher Peterson

Acknowledgements

As the common proverb goes, “It takes a village to raise a child”, and experience tells me that the same wisdom applies to the cultivation of scholarship. It would be hubris to claim my academic accomplishments as solely mine, and it is with pleasure and gratitude that I acknowledge the individuals in my village.

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Dissertation Abstract

Depression is among the world's most debilitating psychiatric illnesses, and often leads to suicide. Consequently, significant resources have been invested towards understanding depression and its underlying mechanisms. While notable research efforts have led to important discoveries, there continues to be questions that remain unanswered. Most importantly, depression research has been largely organized between those who examine depression during wake, and those who investigate depression during sleep. For example, while very robust and compelling research has established that there are changes in sleep architecture associated with depression, how such changes affect the phenomenology of depression is poorly understood. Similarly, psychopathologists typically examine depression without considering how sleep, a major mediator of mood and cognition, affects depressive symptoms. This partitioned approach to research has inadvertently created gaps in our knowledge and presents a unique opportunity for integration and extension of existing evidence that may provide insights into more effective treatments and prevention. In order to address the sleep/wake divide, this three study dissertation compares brain physiology across states of wakefulness and sleep. Additionally, this dissertation also examines how cortical activity during both sleep and wakefulness is related to mood and severity of depressive symptoms. This dissertation also aims to examine the role of sleep not only as a risk for depression, but also a factor in enhancing mental health. In particular, the relationship between psychological resilience and sleep is examined, along with its role in buffering against the negative affective consequences of sleep disruption.

In the first study, brain physiology during wakefulness and sleep were collected using quantitative EEG and related to positive and negative mood in depressed individuals and healthy controls. Results indicated that baseline cortical activity was related to general positive and negative mood, with decreased activity in the beta frequency associated with negative affective experiences (lower positive and higher negative mood). Preliminary evidence

suggested that decreased cortical activity may specifically represent negative low arousal states, such as anhedonia. Results were consistent with previous research indicating that baseline cortical activity may be associated with the amount of cognitive and emotional resources available to the individual that enables effective engagement in desirable activities.

The second study examined two hypotheses regarding sleep in depression, and explored how each hypothesis related to mood in depression. The first hypothesis posits that depression is characterized by a deficit in slow-wave activity representing deep and restorative sleep. The second hypothesis proposes poor sleep in depression results from hyperarousal of the central nervous system causing intrusions of excess high-frequency activity that prevents high quality sleep. Results show that depression may be better characterized by decreased power in the slow-wave activity (predominantly in the delta band). Decreased delta activity was also found to be related to increased symptom severity, as well as depressed and anxious mood. Though no differences in fast-frequency activity were detected in the total sample, depressed women did exhibit a positive relationship between beta activity and depressed mood after accounting for decreased activity in the delta band. This suggests that while depression may be better characterized by a brain deficit in generating adequately restorative sleep, female brains may also experience hyperarousal that is related to increased depression.

In the third study, the relationship between psychological resilience and sleep was examined using the same sample as the first study. Specifically, this study investigated whether psychological resilience can serve as a protective factor against the negative mood consequences of sleep disruption, and whether this buffer effect is less effective in individuals who suffer from depression. Results indicated that existing levels of resilience continue to buffer against negative affective consequences to experimentally disrupted sleep, even in depressed individuals. Higher resilience in healthy controls is also related to less disrupted baseline sleep, suggesting that psychological resilience may be associated with better quality sleep.

Together, these studies provide a foundation to begin bridging the gap between brain physiology during sleep and wakefulness. They indicate that depression may be characterized by decreased cortical activity that may represent the decreased availability of cognitive and

emotional resources during wakefulness, and deficits in generating adequate deep and restorative sleep during the night. Finally, the third study suggests that resilience may buffer against the negative mood consequences of sleep disruption.

CHAPTER 1

General Introduction

Major Depressive Disorder (MDD) is a debilitating psychiatric illness that constitutes the world's leading cause of disability (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006), and is among the mostly costly illnesses in the world both in terms of human suffering and economic burden (Greenberg et al., 2003). While there is heterogeneity in the experience and presentation of MDD, this disorder is generally characterized by persistent low mood or anhedonia, often accompanied by lethargy, decreased motivation, decreased alertness and focus, and sleep difficulties. In the last two decades, emerging research has indicated that sleep difficulties may not only be a symptom of depression, but may contribute to its cause.

Sleep complaints in depression include difficulty falling asleep, difficulty maintaining sleep, early morning awakenings, poor quality sleep, and less commonly, hypersomnia (Breslau, Roth, Rosenthal, & Andreski, 1996). Sleep complaints are also extremely common in depression, with as many as 90% of depressed individuals reporting notable sleep difficulties (Tsuno, Besset, & Ritchie, 2005), and up to 41% reporting symptoms severe enough for a co-morbid diagnosis of insomnia (Stewart et al., 2006). Several studies have suggested that sleep complaints often persist following successful resolution of depressive symptoms, suggesting that sleep difficulties may not simply be a symptom of depression (Ford & Kamerow, 1989; Lustberg & Reynolds, 2000; Reynolds et al., 1997). Furthermore, Reynolds and colleagues (1997) also demonstrated that individuals who continue to report sleep difficulties following depression treatment are at higher risk for relapse into future depressive episodes.

Other evidence also indicates that sleep may play a role in the etiology of depression. Several studies have examined the temporal relationship between sleep disturbances and depression, indicating that those individuals who are reporting insomnia symptoms are 3.5 times more likely to develop depression (Baglioni et al., 2011; Pigeon & Perlis, 2007; D.

Riemann & Voderholzer, 2003). Furthermore, depressed individuals with comorbid insomnia also exhibit prolonged depressive episodes (Riemann, 2009). Finally, studies have also shown that the use of cognitive behavioral therapy for insomnia both as an adjunctive or a stand-alone treatment in depression results in successful alleviation of depression symptoms (Manber et al., 2008, 2011; Riemann, 2009). Together, the plethora of evidence suggests that disruption of sleep is not only an important part of the phenomenology of MDD, it also likely plays a role in the etiology of the disorder.

The sleep/wake divide

While evidence points to an intimate relationship between sleep and depression, there appears to be a gap in our knowledge regarding how brain activity during sleep is related to the experience of depression during wakefulness. For example, while robust and compelling research has established changes in sleep architecture associated with depression (Borbély et al., 1984), how such differences affect the phenomenology of depression has been virtually unexamined. Similarly, psychopathologists typically characterize depression without considering how sleep, a major mediator of mood and cognition, affects depressive symptoms. This partitioned approach to research has inadvertently created gaps in our knowledge of depression and presents a unique opportunity for integration and extension of existing evidence that may provide insights into more effective treatments and prevention.

Early studies examining sleep in depression have focused on describing the gross organization of sleep (also known as polysomnography, or macroarchitecture), such as latency of sleep onset, total sleep time, latency to rapid eye-movement (REM) sleep, along with amount and percentage of non-REM (NREM) sleep. This method relies on visual scoring of sleep EEG, with a standard practice of assigning singular descriptors of sleep across 30-second epochs (e.g., stages 1-4, REM, arousals, etc). Studies examining macroarchitecture in depression have predominantly identified changes in REM sleep, particularly with depressed individuals exhibiting decreased latency to REM sleep, increased duration of the first REM period, and increased density of eye-movements during REM sleep (e.g., Berger & Riemann, 1993). Although abnormalities in REM sleep have been well replicated in the literature, less is known

regarding how the differences in REM sleep relate to the daytime experiences of symptoms of depression.

Recent sleep research in depression has begun focusing on quantitative EEG (qEEG) as an alternative way to describe brain behavior and physiology during sleep. A qEEG approach to sleep characterizes brain physiology via measures of electroencephalogram (EEG) frequencies across the sleep stage domains, which is referred to as sleep microarchitecture (Armitage, Hudson, Trivedi, & Rush, 1995). This approach provides certain advantages over macroarchitecture because it produces more information that is descriptive of brain physiology during sleep. Additionally, this method of quantifying sleep is also more comparable to ways in which brain physiology is characterized during wakefulness, thereby enabling a more direct comparison between the sleeping and waking brain. Despite this opportunity, very few studies have directly examined how cortical activity during sleep is related to cortical activity during wakefulness, and also how cortical activity across sleep and wakefulness is associated with the experience of depression.

Existing research that has examined qEEG variables in sleep have explored two main hypotheses regarding brain physiology during sleep. The first identifies sleep homeostasis as a process that is deficient in depression. This hypothesis was derived from observations that depressed individuals appear to exhibit both decreased slow-wave activity (SWA) during NREM sleep and an abnormal time-course of SWA (e.g., Borbély et al., 1984). SWA is most prominent in stages 3 and 4 (or N3 sleep), and is associated with a deeper and more restorative sleep. SWA is prioritized to occur predominantly during the first half of the night because of its crucial role in brain restoration, and is related to the level of sleep drive that accumulates with the duration of prior wakefulness (Borbély, 1982). Therefore, abnormalities in the amount and time-course of SWA in depression are thought to be related to a brain deficit in the process of restoration (Borbély, 1987). Again, while this body of research has grown over the last three decades, very few studies have provided evidence that speaks to how the deficits in SWA in depression is related to the experience and symptoms of depression.

The second hypothesis regarding brain physiology in depression stems from research that has noted the high co-morbidity between insomnia and depression. Studies have

consistently documented hyperarousal in primary insomnia, indexed by intrusions of excess high frequency activity (i.e., beta band). It is posited that individuals with primary insomnia experience hyperarousal of the central nervous system (for review, see Riemann et al., 2010), resulting in increased tension and difficulty relaxing. This subsequently detracts from the individual's ability to transition into sleep, and disrupts the brain's ability to benefit from restorative slow-wave sleep. As evidence suggests that sleep difficulties may be related to the etiology of depression, hyperarousal has also been posited as a potential mechanism in the etiology of depression. However, fewer studies have directly examined the influence of high frequency activity in depression and its potential relationship with depressive symptom and mood. Additionally, there is also a paucity of studies that examine whether sleep in depression is better characterized by a deficit in the brain's ability to generate adequate restorative sleep, or an excess intrusion of fast frequency activity.

In order to address the gaps in the literature, one aim of this dissertation is to examine how brain physiology during sleep is related to both symptomatology and wake cortical activity in depression. As a mood disorder, positive and negative mood in depression is of particular interest as a dependent variable, in addition to examining symptom severity.

Sleep and positive health

As research in mental health grows, increasing attention is being directed towards examining factors that enhance mental health and human flourishing, rather than a unitary focus on mitigating psychopathology. Similarly, preliminary research in sleep has also begun to focus on the role of sleep in promoting positive aspects of mental health. For example, research has also shown that high quality sleep is linearly related to positive affect (Sonnentag, Binnewies, & Mojza, 2008; Steptoe, O'Donnell, Marmot, & Wardle, 2008). However, few studies have directly examined how mechanisms of sleep are related to wellness and resilience. Resilience is of particular interest because it is related to both the reduction in illness (Khanlou & Wray, 2014), and promotion of human flourishing (Ryff & Singer, 2003). The increasing attention towards positive psychology in mental health research also calls for the investigation for strengths-based interventions in depression (e.g., Sin & Lyubomirsky, 2009). If resilience has

a role in protecting individuals from the risks that accompany sleep disruption, it may also have a cascading effect in preventing not only depression, but a myriad of physical and mental health complications. As such, this dissertation also aims to explore the relationship between resilience and sleep in depression.

Summary

The goal of this three study dissertation is to understand the role sleep plays in the daytime symptoms and neurobiology of depression by bridging the sleep/wake gap. Doing so is important because, despite the evidence suggesting a direct relationship between daytime functioning and sleep, research has largely examined them independently, therefore precluding the ability to detect underlying mechanisms that may improve current interventions. The first two parts of this dissertation examine how brain functioning during sleep influences depression symptoms, daytime mood, and daytime brain functioning. The third part of this dissertation examines how psychological resilience impacts affective consequences of sleep disruption in depression and healthy controls.

Study One

Major depressive disorder (MDD) is often characterized as a loss of vitality, indicated by persistent anhedonia, lethargy, lack of motivation, and decreased concentration, all of which contribute to an inability to “get going” and actively engage in desirable activities. Anterior asymmetry in cortical activity in depression has received wide-spread attention as a potential marker for depression (Debener et al., 2000). However, replication of the anterior asymmetry hypothesis has been inconsistent, especially with the development of advanced neuroimaging techniques, such as positron emission topography and functional magnet resonance imaging. Another line of research has pointed to quantitative EEG (qEEG) as an alternative way of characterizing brain physiology in MDD. Specifically, research has examined cortical activity across different frequencies during a restful waking state as a way of understanding basic brain function.

Study one aimed to compare brain physiology during both wakefulness and sleep, as well as explored how cortical activity related to mood in depression. Very few studies have examined brain physiology across both sleep and wakefulness, which could be resulting in lost opportunities for a more integrated understanding of depression. Participants in this study completed two nights in the laboratory where their EEG activity was recorded during both resting wakefulness and sleep. Participants also completed questionnaires measuring positive and negative mood. Cortical activity during the evening, morning, and during sleep were used as predictors in positive and negative mood in order to characterize how mood in depression is related to brain physiology.

Study Two

The second study is a large archival study that examined how sleep EEG variables are related to depressive symptoms and mood. A notable majority of depressed patients complain of difficulties in falling and staying asleep, and overall poor quality sleep. While there is evidence that such disturbed sleep has a negative impact on daytime functioning, the exact relationship to symptoms of depression remains unclear. Additionally, sleep studies have historically relied on descriptive changes of sleep macroarchitecture (i.e. stage scoring of stages 1-4 and REM), or general organization of sleep. This method is limited in scope because the assignment of singular sleep stages to 30 second epochs does not capture the multiple EEG events that could have transpired. Additionally, evidence suggests that quantifying sleep in discreetly bounded stages may not be ecologically valid.

Instead, this study used a frequency-domain based approach using Fast Fourier Transform (FFT) which allows for the digital analysis of data that is a more fine-grained description of brain physiology via measures of EEG frequencies and amplitudes across the sleep stage domains. This approach better captures dysfunctions of brain processing that may contribute to the disorder (Armitage, Hoffmann, Loewy, & Moffitt, 1989). Studies using quantitative EEG have suggested that complaints of poor sleep quality may be related to deficits of the sleep homeostatic system in producing effective recovery sleep, thereby resulting in hyperarousal of the central nervous system during the night (Armitage & Hoffmann, 2001;

Armitage & Hoffmann, 1997; Mendelson, James, Garnett, Sack, & Rosenthal, 1986; Stepanski, Zorick, Roehrs, & Young, 1988). In order to test this hypothesis, this study takes a quantitative EEG approach to explore how EEG activity across the night impacts depressive symptoms experienced during wakefulness.

The sample from this second study was extracted from archival sleep data collected from the University of Texas Southwestern Medical School and University of Michigan. A total of 150 participants (75 depressed, 75 healthy controls) were randomly selected for inclusion in this study. Quantitative EEG from several frequencies across each hour of the night were calculated and compared between those with MDD and healthy controls (HC). Additionally, these frequencies were entered into a regression model as predictors for depression severity and mood. If brain functioning during sleep is related to emotional-functioning during wakefulness, EEG activity during sleep should significantly predict variations in mood and symptom severity.

Study Three

The third study examines the relationship between sleep variables and psychological resilience. Psychological resilience is characterized by the ability to respond and recover from environmental stressors (Block & Kremen, 1996). Though research has established several personality and psychological traits that are associated with resilience, less research has considered how resilience may affect sleep processes. Sleep is important to consider because research has identified its importance in emotional experiences and regulation (Walker & van der Helm, 2009), suggesting that a strong sleep system can contribute significantly to the resilience.

In this study, participants are exposed to an environmental stressor via one night of sleep disruption. Participants in this study completed a measure of resilience, and positive and negative mood before and after two different sleep conditions: baseline sleep, and slow-wave sleep interruption. During the slow-wave sleep interruption condition, delta waves were visually detected and subsequently interrupted using a series of tones. These tones were delivered using a protocol that maximizes disruption to slow-wave activity without waking the

participant. Analyses examined whether reported resilience is related to attenuations of negative affective consequences of sleep interruption, and if this attenuation differs by depressed or healthy control groups. Exploratory correlations were also conducted to examine how sleep is related to higher resilience in healthy individuals.

In sum, these three studies will determine: 1) how brain functioning during sleep and wakefulness, as indexed by EEG, predicts depression symptoms and mood, 2) if sleep in depression is better characterized by decreased slow-wave activity, or intrusions of excessive fast-frequency activity, and finally 3) if psychological resilience can serve as a buffer against negative affective consequences of sleep disruption. These studies integrate and extend existing but separate research in depression, and provide a foundation for understanding how depression and well-being is impacted by sleep.

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CHAPTER 2

Mood and Cortical Activity across Wakefulness and NREM sleep in Major Depression

Introduction

Major depressive disorder (MDD) is often characterized as a loss of vitality, indicated by persistent anhedonia, lethargy, lack of motivation, and decreased concentration, all of which contribute to an inability to “get going” and actively engage in desirable activities. In order to further understand the mechanism driving these symptoms of depression, research in the last two decades has increasingly focused on neurophysiological substrates of depression. Much of this research has focused on electroencephalography (EEG) as a tool in characterizing brain physiology in depression. While research has predominantly involved the examination of asymmetrical activity in the frontal cortex as an index of emotional reactivity, others have also employed alternative methods of quantitative EEG in understanding the brain in depression.

Anterior asymmetry in cortical activity in depression has received wide-spread attention at a potential marker for depression (Debener et al., 2000). This asymmetry was based on early studies documenting that lesion patients exhibited enhanced positive emotions when lesions were located in the right-hemisphere (Starkstein et al., 1989), and displayed undue negative affect when lesions were located in the left-hemisphere (Gainotti, 1972). Though many studies have documented anterior asymmetry in depression (for review, see Davidson, 1992), it has not been invariably replicated (e.g., Baskaran, Milev, & McIntyre, 2012; Kentgen et al., 2000; Reid, Duke, & Allen, 1998). Similarly, additional lesion studies have also yielded conflicting results, with some studies failing to replicate the association between left anterior lesions and subsequent depression (e.g., Dam, Pedersen, & Ahlgren, 1989; Herrmann, Bartels, Schumacher, & Wallesch, 1995; House, Dennis, Warlow, Hawton, & Molyneux, 1990). Furthermore, studies

utilizing functional magnetic resonance imaging and positron emission tomography have largely failed in identifying hemispheric asymmetries in underlying neural substrates, leading some researchers to question the validity of the frontal asymmetry hypothesis (e.g., Murphy, Nimmo-Smith, & Lawrence, 2003; Wager, Phan, Liberzon, & Taylor, 2003).

An alternative way of characterizing brain physiology in MDD is examining and comparing EEG activity across different frequencies during a restful waking state. Alpha activity (roughly 8-12Hz) is often of interest because it is associated with mental relaxation, and used as an inverse index for cortical arousal (Gevins, 1998). Beta activity (roughly 16 – 32 Hz) is also of interest because it is also associated with electrophysiological arousal that indicates increased cognitive activity, such as alertness and attention (Berger, 1931; Gola, Magnuski, Szumska, & Wróbel, 2013; Niedermeyer, 1999). Sigma activity (roughly 12-16 Hz) is traditionally used in sleep EEG to identify spindle activity, though this frequency is also sometimes categorized as a lower-frequency beta activity during wakefulness. Theta (roughly 4 – 8 Hz) and Delta activity (roughly 0.5 – 4 Hz) are considered slower frequency activity that are more pronounced during deeper and more restorative sleep. General theta activity across the scalp during wake has been associated with low-level alertness that may indicate inefficient information process or drowsiness (Schacter, 1977). Delta activity during wakefulness has been related to brain dysfunction, such as inefficient perfusion and metabolism (Howland, Shutt, Berman, Spotts, & Denko, 2011).

Studies have documented some qEEG differences between depressed and healthy individuals. Early research suggested that depressed individuals may experience increased fast frequency activity (beta or higher), and decreased slow frequency activity (delta) compared to healthy individuals, though these results were not consistently replicated (Pollock & Schneider, 1990). Later studies have suggested that increased beta activity in waking EEG may be associated with response to a range of psychoactive medications (Coutin-Churchman et al., 2003; Wauquier, 1993). Other studies have also pointed to an increased in alpha activity in depression (Brenner et al., 1986; John, Prichep, Fridman, & Easton, 1988; Schaffer, Davidson, & Saron, 1983).

In addition to understanding brain physiology during wakefulness, it is also equally important to examine brain physiology during sleep. As both a symptom and a risk factor for depression (Clarke & Harvey, 2012; Haynes, Ancoli-Israel, Walter, & McQuaid, 2012), sleep and its underlying neurophysiology is of particular importance in depression. In addition to difficulty falling and staying asleep, depressed individuals also commonly report light or restless sleep, and waking up feeling tired and unrestored. This is consistent with evidence that depressed individuals show reduced delta activity and increased beta activity in depression (for review, see Armitage et al., 1995). Furthermore, a recent study in depression has also found that variation in reports of restfulness in the morning is predicted by the amount of activity in the slow wave, or delta frequency (see CHAPTER 3). Several studies have also indicated that quality of sleep influences positive and negative mood in the following day (Hamilton et al., 2008; Sonnentag et al., 2008; Steptoe et al., 2008); however, very few studies have looked at how qEEG in depression as related to positive and negative mood.

While the identification of group differences in brain physiology have contributed to important advances towards establishing biomarkers of psychopathology, more work is needed in understanding what psychological factors these variables may represent. As a mood disorder, positive and negative mood is of particular interest in depression. Previous research has suggested that mood may be related to increased baseline cortical activity, which may represent the amount of cognitive resources available to the individual. Specifically, one study examining factors predicting response to a brief cognitive intervention identified increased baseline cortical activity, indexed by decreased alpha activity, as a significant predictor of positive mood (Deldin & Chiu, 2005). The authors proposed that global cortical arousal may be a task-independent factor that is associated with general affective reactivity.

In order to address the gaps in the literature, the current study aims to compare brain physiology across the different frequencies between groups, and also examine the relationship between positive and negative mood and brain physiology in depression. Very few studies have examined brain physiology across both sleep and wakefulness, which could be resulting in lost opportunities for a more integrated understanding of depression. To that end, EEG activity from resting wakefulness and across non rapid eye movement (NREM) sleep were collected and

quantified across five frequency bands ranging from slow (delta) to fast (beta) frequency activity. Sleep EEG was limited to NREM sleep periods due to its specific function in generating restorative sleep, and may also likely relate to mood. Based on previous research, it was hypothesized that depressed individuals would show decreased cortical arousal indexed by increased alpha activity, decreased beta activity, and increased delta activity. Additionally, it was hypothesized that increased cortical arousal, indexed by either increased beta activity or decreased alpha activity during wakefulness would be related to positive mood consequences represented by either increased positive mood, or decreased negative mood. If the depressed group exhibit excessive beta activity compared to the healthy control group during sleep, we anticipated that increased beta activity during sleep would be associated with poor mood consequences, represented by either increased negative mood, or decreased positive mood. Based on research describing decreased slow-wave activity in depression, it was also hypothesized that decreased delta activity would be associated with poor mood consequences, represented by either increased negative mood, or decreased positive mood.

Methods

Participants

A total of 34 participants (19 females) between the ages of 18 and 50 years old were recruited from the community via fliers and included in this study. Eighteen of these participants were healthy controls with no psychiatric history and do not meet diagnostic criteria for any Axis I disorder. No differences in age was detected between the healthy control group (mean = 26.8, SD = 9.3) and the depression group (mean = 26.0, SD = 9.2). Healthy controls also required a Beck Depression Inventory II (BDI-II; Beck et al., 1996) score of less than seven. Sixteen of these participants were individuals who meet criteria for Major Depressive Episode based on DSM-IV-TR criteria, with a BDI-II score of at least 14. The depressed and healthy control groups did not differ in sex or age. BDI-II scores for the depressed group indicated moderate levels of depression severity (mean = 23, SD = 6.5), compared to very low depression in the healthy control group (mean = 1.94, SD = 2.8).

Procedures and recruitment for this study comply with the ethical standards of the Institutional Review Board.

Participants in this study were recruited as part of a larger study investigating the cognitive consequences of sleep disturbance in depression. Exclusionary criteria in this study included history of head injury resulting in loss of consciousness longer than 2 minutes, neurological diseases, use of psychotropic medications, and co-occurrence of independent sleep disorders (e.g., insomnia, obstructive sleep apnea, narcolepsy, restless leg syndrome, and bruxism). Participants were also excluded for lifetime histories of substance dependence, bipolar I or II disorder, psychosis, and anorexia or bulimia. Participants received \$10 for each hour of screening, and \$75 for each night of research participation.

Procedure

Participants

Participants were recruited from the community in a medium-sized mid-western city. All participants were screened for presence and history of psychiatric disorders using the Structured Clinical Interview for the DSM-IV (SCID-I/NP; First, 2007). This interview was conducted by a trained graduate student and/or a doctoral-level clinical psychologist. Participants were excluded from the study if they report any significant illnesses (e.g. untreated hypothyroidism), any lifetime history of DSM-IV Axis-I disorder for the healthy control group, or head trauma resulting in two minutes or more of unconsciousness. All ethical and informed consent guidelines are approved by the Institutional Review Board.

Experimental Conditions

Each participant completed two nights (adaptation, baseline) with acquisition of polysomnography. Prior to the first night, participants were asked to maintain five nights of a regular sleep schedule consistent with the sleep schedule during the study. Sleep schedules were approximated to the participants' natural sleep schedule at the time of recruitment. Compliance with the schedule was monitored through sleep diary and actigraphy (measurement of light and motion). Any deviations from their designated schedule that were greater than 2 hours prior to their first night were grounds for study exclusion. Additionally,

participants were asked to refrain from use of caffeine after 12 noon, and abstain from alcohol or drug use. This pre-study period was followed by three consecutive nights in the sleep laboratory, with the first night serving as adaptation to the new sleep environment and as a screening for independent sleep disorders.

Behavioral Tasks

Participants also completed a series of resting state tasks before and after sleep on the baseline night. During this task, participants were instructed to relax while their EEG was being recorded. The resting EEG task included two blocks presented in random order; one six minutes eyes-open and one six minutes eyes-closed block. During the eyes-open block, participants were instructed to keep their eyes on the fixation cross, and to avoid thinking about anything in particular. During the eyes-closed block, participants completed the same task with their eyes closed, but without falling asleep. Each participant completed the resting EEG task before and after sleep for each night in the laboratory.

Mood measures were also completed before and after sleep on baseline night. Mood was measured via the Visual Analogue Scale (VAS) with separate items for positive and negative mood. Participants also completed a version of the Beck Depression Inventory (BDI-II; Beck et al., 1996) modified to assess current symptoms instead of symptoms within the last two weeks.

Post-hoc measures were also included in this study to examine convergent evidence for constructs similar to or involving positive and negative mood. Questionnaires were completed on or prior to the first night in the lab, before any experimental tasks were administered. Questionnaires included the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988), Life Orientation Test (LOT, a measure of optimism; Scheier & Carver, 1985), Ego-Resilience Scale (ER89, a measure of psychological resilience; Block & Kremen, 1996), and Mood and Anxiety Symptom Questionnaire (MASQ; Watson & Clark, 1991) Anxious Arousal and Anhedonia subscales.

Physiological Data

Sleep polysomnography recording included eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2) with placement according to the International 10-20 system. Two electrooculogram (EOG) electrodes were placed at the left suborbital and right supraorbital ridges.

Electromyogram consisted of bipolar chin and cheek electrodes. Impedance for scalp and face electrodes were kept below 2 KOhms and 5 KOhms respectively. With the exception of the Electromyogram (EMG), all electrodes were referenced to linked electrodes placed at the left and right earlobes and passed through a 10 KOhm resistor.

Wake electroencephalogram were recorded with nine scalp electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) with placement according to the International 10-20 system. Electroculogram consisted of two electrodes placed lateral to the left canthus and above the right supraorbital ridge. Impedance and references were identical to that of sleep polysomnography.

Physiological data were recorded using a Vitaport digital ambulatory system (TEMEC Instruments, Kerkrade, Netherlands), with a sampling rate of 256 Hz and amplified by 2500, and filters set from 0.16 Hz to 70 Hz. EOG data were sampled at 64 Hz, amplified by 2500, and filters set from 0.16 Hz to 30 Hz. EMG data were sampled at 64 Hz, amplified by 5000, with filters set from 0.16 Hz to 70 Hz. Additionally, a 60 Hz notch filter was applied to reduce electrical noise. Sleep records were visually scored by research personnel in accordance with standard criteria (Rechtschaffen & Kales, 1968). Scoring personnel were trained for a 90% stage agreement or higher on an epoch-by-epoch basis. All records were inspected visually and epochs containing movement, breathing or muscle artifact, or recording difficulties were excluded from analysis.

Following data collection, EEG power was quantified across five frequencies using power spectral analysis (PSA), which uses a set of sine and cosine functions to capture EEG activity occurring between discrete frequencies. PSA generates numerical representations of EEG that is based on amplitude of EEG activity as well as duration of rhythmic activity. PSA is based on the use of fast Fourier Transform (FFT; Gottman, 1981), which is a commonly used strategy for EEG analysis (Campbell, 2009). FFT analyses were conducted for the following five frequencies: delta (0.5 Hz to < 4 Hz), theta (4Hz to < 8Hz), alpha (8 Hz to < 12 Hz), sigma (12 Hz to < 16 Hz), and beta (16 Hz to < 32 Hz). EEG data were averaged between eyes-open and eyes-closed

condition in the main analyses in order to preserve power, and because no hypotheses were generated regarding differences between the eyes-open and eyes-closed conditions,.

Statistical Analyses

Prior to hypothesis testing, analyses were conducted to verify the consistency of the data with the literature, as well as to provide basic descriptive data of the variables. To that end, scalp distribution of alpha activity was examined to demonstrate increased alpha activity in the parietal region relative to the frontal region, and also to demonstrate increased power during the eyes-closed versus the eyes-open condition. Although this study focused on quantitative EEG (qEEG), polysomnography variables were also presented and tested for differences between groups for comparison with previous research. Finally, correlations were completed between the EEG and mood variables to provide descriptive data regarding the relationship between the independent variables.

Due to the plethora of EEG variables (pre- and post-sleep wake EEG, in addition to NREM sleep EEG across five frequencies), a 3-way repeated measures ANOVA was first conducted to establish differences between the variables and to test for significant differences between groups. EEG activity was submitted as the dependent variable to a Condition (PM, NREM Sleep, AM) \times Frequency (Beta, Sigma, Alpha, Theta, Delta) \times Group (MDD, HC) repeated measures ANOVA. A priori contrasts were set for comparison between cortical activity recorded before bed (PM) and following sleep (AM) to test for differences pre- and post-sleep. In the case that no differences were detected, EEG variables were to be averaged between pre- and post-sleep conditions to preserve power in subsequent analyses. Similarly, a priori contrasts were also set for comparison between sleep and wake EEG in order to further validate data quality. Results are expected to reveal a Condition (sleep versus wake) \times Frequency interaction that indicates greatest differences in the delta frequency during sleep.

Mood data were also examined in order to determine if positive and negative mood differed pre- and post-sleep. Scores on the VAS were also submitted to a Valence (positive, negative) \times Time (PM, AM) \times Group (MDD, HC) 3-way repeated measures ANOVA. As with the EEG variables, in the case that no differences were detected between pre- and post-sleep mood

measures, an average were to be calculated between the pre- and post-sleep conditions to preserve power in subsequent analyses.

In order to test the hypothesis that increased cortical activity is related to mood, regression analyses were conducted with beta and alpha activity during wake and sleep as predictors, and positive and negative mood as the dependent variables. In order to test the hypothesis that decreased slow-wave activity is related to mood, regression analyses were also conducted with delta activity during wake and sleep as predictors, and positive and negative mood as the dependent variables. Based on results of the regressions, post-hoc comparisons with other measures similar to or involving positive and negative mood were also conducted in attempt to acquire convergent evidence for the relationship between cortical activity and mood.

Results

Descriptive Data

EEG Topography

In order to confirm the consistency of our data with that reported in the literature, we examined the distribution of alpha power across the scalp. An ANOVA examining Diagnosis \times Region \times Eyes revealed a main effect of Region $F(1,30)=18.795$, $p<.001$, indicating that EEG alpha was greater in the parietal regions compared to frontal regions, as expected (see Figure 2.1). Analyses also revealed a main effect of Eyes, $F(1,30)=31.948$, $p<.001$, indicating that alpha power was greater during the eyes closed condition.

Sleep Characteristics

Although this study focused on qEEG variables, polysomnography was also examined for any sleep abnormalities and comparison to differences in sleep architecture found in previous depression studies. Independent one-way ANOVAs were conducted on polysomnographic variables (see Table 2.1). Results showed a difference in REM latency that was approaching statistical significance, with the MDD group demonstrating a shorter latency to REM sleep, as is consistent with the literature. No abnormalities in sleep were detected.

Descriptive Correlations

Correlations were conducted in order to describe the relationships between the experimental variables. Initial relationships appear to suggest that increased cortical activity, especially in the faster frequencies (i.e., beta and sigma) are moderately to strongly related to increased positive mood and decreased negative mood (see Table 2.2Table 2.3Table 2.4)

Differences in Cortical Activity

A three-way repeated measures ANOVA was conducted in order to examine differences in cortical activity by Condition (PM, AM, NREM Sleep), Frequency (Beta, Sigma, Alpha, Theta, Delta), and Group (MDD, HC). No group differences were detected, though the means of the baseline wake EEG variables indicated that they are in the same direction as expected based on previous literature: lower delta activity in the depressed group (mean = 19.5, SE = 3.1) compared to the healthy control group (mean = 20.7, SE = 3.1), and higher alpha activity in the depressed group (mean = 19.7, SE = 4.6) compared to the healthy control group (mean = 16.6, SE = 5.6). The same trend was observed in delta activity during NREM sleep, with the healthy control group showing higher delta activity (mean = 456.1, SE = 29.0) compared to the depressed group (mean = 438.0, SE = 29.0). The lack of group differences may be related to the small sample size, which is further discussed in the limitations section.

In order to examine differences in wake cortical activity by time of day, contrasts were set a priori comparing EEG collected before and after sleep. Results did not reveal a Condition (AM versus PM) \times Frequency interaction, indicating that cortical activity in each of the five frequencies did not differ based on nighttime or morning recording conditions. Based on this result, wake EEG variables were averaged across AM and PM conditions for subsequent analyses. Similarly, a priori contrasts were also set in order to compare wake versus sleep cortical activity across different frequencies. Results revealed that cortical activity differed by wakefulness versus NREM sleep, Condition (wake versus sleep) \times Frequency, $F(1,28)=439.57$, $p < .001$. As expected, differences were most pronounced in the delta frequency, and least difference in beta frequency.

Differences in Positive and Negative Mood

A three-way repeated measures ANOVA was also conducted in order to examine differences in mood by Time (PM, AM), Valence (Positive, Negative), and Group (MDD, HC). As expected, results revealed that differences between positive and negative mood differed by group, Valence × Group interaction, $F(1,31)=33.170$, $p < .001$. While the HC group exhibited a large difference between positive (mean = 71.67, SE = 2.18) and negative (mean = 21.97 SE = 3.26), the MDD showed similar levels of positive (mean = 49.13, SE = 3.28) and negative (mean = 50.16, SE = 3.36) mood. No significant main effects or interactions with Time were detected. Based on this result, positive and negative mood were average across AM and PM conditions in subsequent analyses.

Cortical Predictors of Mood

In order to test the relationship between cortical arousal and mood, two sets of regressions were completed (see Table 2.5 Table 2.6 **Error! Reference source not found.**). For positive and negative mood respectively, linear regressions were performed with beta and alpha activity from both wakefulness and NREM sleep as predictors. Results revealed that beta activity during both wakefulness and NREM sleep significantly predicted increased positive mood. Only beta activity during wakefulness predicted decreased negative mood. Alpha activity did not significantly predict mood.

In order to test the relationship between slow-wave activity and mood, regressions were also conducted with delta activity from both wakefulness and NREM sleep as predictors of positive and negative mood. Contrary to our hypothesis, delta activity was not a significant predictor of mood.

Based on these results, beta activity was use in post-hoc comparisons with other measures that approximate positive and negative mood in order to examine convergent evidence (see Table 2.7 and Table **2.8**).

Positive Items. Items selected for comparison to the positive VAS scale included the positive affect subscale from the Positive and Negative Affect Schedule (PANAS), the Life Orientation Test (LOT; a measure of optimism), and the Ego-resilience Scale (ER89; a measure

of psychological resilience). Results from the total sample suggest that beta activity across both wakefulness and NREM sleep were positively correlated with positive mood. Correlations were also comparable in direction and strength with the PANAS positive subscale, the LOT, and the ER89. The depressed participants showed strong positive correlations between beta activity during wakefulness and positive mood on both the VAS and PANAS. The healthy control group showed medium to strong positive correlations to positive mood on the VAS across wakefulness and NREM sleep, with similarly positive and medium to strong correlations with positive mood on the PANAS, LOT, and ER89.

Negative Items. Items selected for comparison to the negative VAS scale included the negative affect subscale from the Positive and Negative Affect Schedule (PANAS), and the Anxiety Arousal and Anhedonia subscales from the Mood and Anxiety Symptom Questionnaire (MASQ). Results revealed that beta activity across NREM sleep and wakefulness were negatively correlated at medium strength with negative mood in the total sample. Correlations in the depressed group show similar direction and strength in beta activity.

Interestingly, correlations in the healthy control group were negative for waking beta activity and negative mood on the VAS, but positive for waking beta and negative mood on the PANAS. Statistical comparison using the Fischer's r-to-z transformation (Meng, Rosenthal, & Rubin, 1992) revealed that these correlations were significantly different from each other ($p < .01$). A closer look at individual items on the PANAS negative subscale suggest that the negative items represent higher arousal emotions, such as "distressed", "hostile", "irritable", "jittery", "scared", and "upset", which may explain the positive correlation with increased fast frequency activity. In order to further explore this, correlations were also compared to the Anxious Arousal and Anhedonia subscales of the MASQ. Results in the healthy control group also reveal that beta activity in NREMP sleep were positively related to Anxious Arousal, but negatively related to Anhedonia. Fischer's r-to-z transformation reveals that all correlations between NREMP cortical activity and Anxious Arousal versus Anhedonia are significantly different (all $p < .01$). Together, this may indicate that in healthy individuals, fast frequency activity during wakefulness could also be related to higher arousal negative affect, while the decrease in general cortical activity may be related to low arousal negative affect.

Correlations within the MDD group revealed that beta activity during wakefulness were strongly correlated negatively with negative mood on the VAS, but less strongly correlated with negative mood on the PANAS. Further comparisons to anhedonia versus anxious arousal suggests that faster frequency activity may be more related to negative affect that is lower rather than higher arousal. Together, this may indicate that decreased EEG activity during wakefulness in depression may be related to increased lower arousal negative affect.

Beta activity and sleep quality. In order to compare results with beta activity to the findings in the insomnia literature, post-hoc analyses were also conducted with sleep quality and restfulness in the morning from the sleep diary. Correlations were conducted using Spearman's rho coefficient because both items were scored on the ordinal scale. Results indicate that increased beta activity during evening wakefulness is also positively related to sleep quality and restfulness in the morning (see Table 2.9).

Similar results were found using beta activity during morning wakefulness, with higher beta activity related to higher sleep quality, and restfulness in the morning. Results did not show significant relationships between sleep quality and restfulness in the morning with beta activity during NREM sleep, though the coefficients were also positive.

Discussion

This study aimed to characterize the relationship between brain physiology and mood across states of resting wakefulness and NREM sleep in depression. Taken together, results from this study suggest that positive and negative mood in depression may be associated with the availability of brain resources as represented by increased cortical activity in the beta band across sleep and wakefulness.

Results in this study demonstrated that higher beta activity was associated with increased positive mood and decreased negative mood in depressed and healthy control participants. Beta activity during wakefulness has been associated with increased cognitive attention, alertness and attention (Berger, 1931; Gola, Magnuski, Szumska, & Wróbel, 2013;

Niedermeyer, 1999). Therefore, one interpretation of this result may be that individuals exhibiting higher cortical activity may have more cognitive resources available, and in turn may enable them to more effectively engage in desirable activities. This result is consistent with a previous study demonstrating that depressed participants with higher baseline cortical activity are more likely to experience increased happiness following a brief cognitive intervention (Deldin & Chiu, 2005). In fact, the authors of this study proposed that global cortical activity may be an important index of affective reactivity has thus far been largely neglected.

While this study predominantly examined mood by valence (positive and negative), there is some preliminary evidence that increased cortical activity may also represent arousal of affect. Specifically, healthy controls also exhibited a positive association between cortical activity and negative mood as measured by the PANAS, but not as measured by the VAS. Comparison of the PANAS and VAS showed that items on the PANAS may represent negative affect that are higher on arousal, such as “distressed”, “irritable”, and “jittery”, whereas the VAS measured generally negative mood. Comparisons also indicated that depressed participants reporting higher anhedonia also exhibited decreased beta activity. Anhedonia represents a reduction or lack of pleasure, and is often clinically accompanied by reduced motivation, both of which indicate that anhedonia would be considered a state of lower arousal. Together, this also further suggests that decreased cortical activity may be associated with lower cognitive and emotional resources, which would be consistent with several characteristics of depression, including anhedonia, reduced motivation, decreased concentration, and lethargy.

Post-hoc analyses comparing beta activity during NREM sleep with sleep quality and restfulness in the morning also revealed that increased beta activity in NREM sleep is related to better quality sleep and increased restfulness in the morning. Although this is consistent with the other results in this study, these results may be somewhat unexpected compared to previous findings of elevated beta activity in patients with Primary Insomnia (Perlis, Merica, Smith, & Giles, 2001). However, it is important to note that individuals in this study were excluded from participation if they reported or demonstrated moderate to severe sleep difficulties or insomnia. In fact, the sleep efficiencies in both groups suggest that participants in

this sample are relatively good sleepers. Therefore, it may be the case that barring excessive arousal as indicated in Primary Insomnia, higher beta activity in depression may represent a healthier amount of cortical activity that promotes alertness, restfulness, increased positive mood, and decreased negative mood.

Finally, regression analyses also indicated that beta activity across both resting wakefulness and NREM sleep predicted increased positive mood, indicating that brain activity during both sleep and wakefulness may be an important indicator of the availability of brain resources that influence mood in depression.

Limitations

Limitations of this study include the smaller sample size, which explain the lack of statistically significant group differences detected. However, it is important to note that recruitment for this study precluded participants who reported or demonstrated moderate to severe sleep difficulties, resulting in a sample of relatively and comparably good sleepers. It is possible that the selection of good sleepers may have obscured any group differences that would otherwise have been detected. Results also did not show significant differences in delta activity across the night. This may also be related to a smaller sample size. Future comparisons may include examination of delta activity during the first NREM period as well as change across subsequent NREM periods.

Secondly, while results in this study suggested that cortical activity may represent arousal and valence of affect, this would require further evidence to be conclusive. This study did not directly compare both arousal and valence in affect, and therefore cannot say with certainty that arousal is an important factor in cortical activity. Further research would be required to examine this hypothesis.

Conclusion

The current study examined the relationship between mood and cortical activity during sleep and wakefulness in both depressed and healthy participants. Consistent with previous research, results suggest that increased baseline cortical activity in both wake and NREM sleep

are associated with increased positive mood and decreased negative mood. Furthermore, decreased cortical activity may be associated with a lack of cognitive and emotional resources, and therefore may also be related to the experience of negative low arousal states such as anhedonia and amotivation. Future research may examine changes in mood based on experimental manipulation of sleep.

Appendix

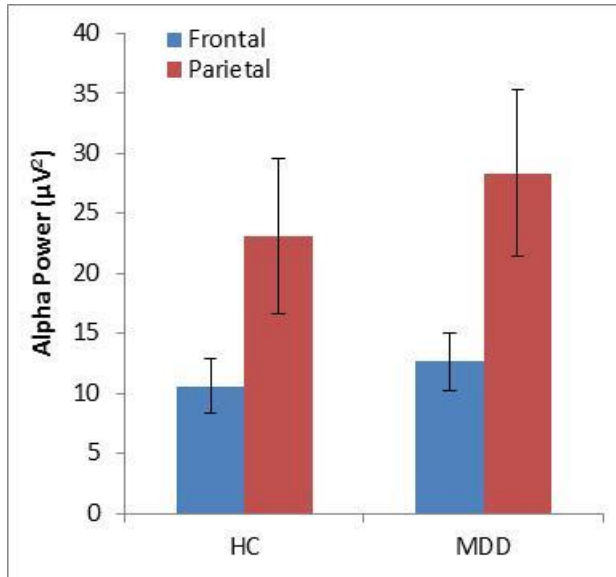


Figure 2.1. Alpha power in the frontal and parietal regions by group.

	HC (N=16)	MDD (N=16)	F-test
<i>Total sleep time (minutes)</i>	412.5 (28.6)	398.8 (41.2)	ns
<i>Sleep onset latency (minutes)</i>	7.4 (6.8)	10.2 (6.8)	ns
<i>Stage 1% (N1)</i>	4.4 (3.0)	4.1 (2.8)	ns
<i>Stage 2% (N2)</i>	52.2 (9.2)	51.7 (7.0)	ns
<i>Stages 3% and 4% (N3)</i>	16.1 (6.3)	16.6 (7.7)	ns
<i>%REM</i>	24.3 (8.6)	24.6 (4.8)	ns
<i>REM latency (minutes)</i>	98.1 (55.6)	63.6 (44.6)	$p = .062$
<i>Awake and moving %</i>	2.9 (1.4)	3.0 (1.6)	ns
<i>Sleep efficiency %</i>	95.1 (2.2)	94.5 (2.3)	ns

Table 2.1 Polysomnographic variables by group.

	Total Sample				Depressed Group				Healthy Control Group			
	Positive PM	Negative PM	Positive AM	Negative AM	Positive PM	Negative PM	Positive AM	Negative AM	Positive PM	Negative PM	Positive AM	Negative AM
<i>Beta - Wake PM</i>	.381*	-.287	.457**	-.433*	.526*	-.341	.550*	-.623**	.268	-.265	.442 [†]	-.379
<i>Beta - Sleep NREM</i>	.485**	-.447*	.406*	-.250	.183	-.228	.161	-.081	.616*	-.511*	.439 [†]	-.149
<i>Beta - Wake AM</i>	.379*	-.309 [†]	.380*	-.303 [†]	.503 [†]	-.323	.568*	-.591*	.354	-.415	.349	-.148
<i>Sigma - Wake PM</i>	.286	-.268	.368*	-.398*	.505*	-.385	.540*	-.593*	.119	-.285	.312	-.409 [†]
<i>Sigma - Sleep NREM</i>	.517**	-.437*	.438*	-.209	.499*	-.451 [†]	.474 [†]	-.311	.511*	-.397	.422 [†]	.037
<i>Sigma - Wake AM</i>	.264	-.268	.333 [†]	-.310 [†]	.491 [†]	-.362	.548*	-.558*	.037	-.238	.202	-.143
<i>Alpha - Wake PM</i>	.092	.017	.214	-.148	.388	-.235	.422	-.438 [†]	-.076	.115	.351	-.204
<i>Alpha - Sleep NREM</i>	.322 [†]	-.287	.379*	-.234	.356	-.233	.468 [†]	-.386	.181	-.275	.296	.118
<i>Alpha - Wake AM</i>	.077	.015	.215	-.158	.376	-.220	.542*	-.492	-.155	.095	.214	-.140
<i>Theta - Wake PM</i>	.122	-.110	.180	-.112	.343	-.146	-.245	-.029	-.026	-.078	.429 [†]	-.189
<i>Theta - Sleep NREM</i>	.376*	-.371*	.312 [†]	-.164	.187	-.143	-.051	.032	.485 [†]	-.529*	.526*	-.171
<i>Theta - Wake AM</i>	.034	-.007	.101	.009	.152	.032	-.006	-.054	.113	-.220	.477*	-.240
<i>Delta - Wake PM</i>	-.015	-.020	.052	-.045	-.127	.397	-.294	.101	.016	-.292	.272	-.119
<i>Delta - Sleep NREM</i>	.079	-.121	.037	.070	-.118	.019	-.351	.321	.255	-.250	.328	-.025
<i>Delta - Wake AM</i>	-.057	.074	.028	.066	-.066	.297	-.097	-.047	.140	-.294	.421 [†]	-.147

Table 2.2. Correlations (Pearson's r) between VAS mood scales and Sleep/Wake EEG variables. [†]p≤.1, * p≤.05, ** p≤.01

	Total Sample					Depressed Group					Healthy Control Group				
	Beta AM	Sigma AM	Alpha AM	Theta AM	Delta AM	Beta AM	Sigma AM	Alpha AM	Theta AM	Delta AM	Beta AM	Sigma AM	Alpha AM	Theta AM	Delta AM
Beta PM	.906**	.788**	.609**	.206	.269	.981**	.915**	.826**	.108	.126	.832**	.651**	.310	.281	.416
Sigma PM	.795**	.909**	.636**	.119	.172	.911**	.989**	.913**	.088	-.173	.671**	.823**	.274	.138	.518*
Alpha PM	.686**	.767**	.926**	.249	.009	.866**	.945**	.970**	.114	-.174	.526*	.583*	.826**	.470	.333
Theta PM	.183	.074	.378*	.770**	.208	.057	.069	.186	.778**	.169	.354	.113	.639**	.807**	.264
Delta PM	.143	-.107	-.011	.435*	.468**	-.010	-.274	-.254	.287	.726**	.353	.082	.283	.564*	.263

Table 2.3. Correlations between wake EEG in the evening and in the morning. † p≤.1, * p≤.05, ** p≤.01, *** p≤.001

	Total Sample					Depressed Group					Healthy Control Group				
	Beta NREM	Sigma NREM	Alpha NREM	Theta NREM	Delta NREM	Beta NREM	Sigma NREM	Alpha NREM	Theta NREM	Delta NREM	Beta NREM	Sigma NREM	Alpha NREM	Theta NREM	Delta NREM
Beta PM	.194	.306	.401*	.099	.180	.114	.526*	.623**	-.022	-.363	.190	.051	.046	.158	.049
Beta AM	.337 [†]	.489**	.544**	-.153	-.081	.156	.574*	.665**	-.002	-.314	.457 [†]	.363	.313	.341	.204
Sigma PM	.061	.275	.501**	.099	.198	.235	.669**	.812**	.262	-.168	-.085	-.143	.024	-.085	-.123
Sigma AM	.205	.478**	.668**	-.140	-.018	.290	.725**	.868**	.315	-.101	.112	.174	.333	.033	.059
Alpha PM	-.024	.199	.545**	.232	.096	.187	.524*	.707**	.285	-.105	-.174	-.229	.246	.223	-.020
Alpha AM	-.074	.172	.541**	-.076	-.206	.243	.596*	.779**	.281	-.106	-.385	-.513*	-.015	-.152	-.405
Theta PM	.077	.019	.162	.391*	.550**	-.061	-.178	-.143	.272	.292	.123	.137	.486 [†]	.470 [†]	.281
Theta AM	.271	.097	.212	.277	.462**	.226	-.028	.021	.410	.464 [†]	.367	.258	.548*	.735**	.497
Delta PM	-.071	-.135	-.115	-.143	.200	-.333	-.379	-.377	-.415	-.162	.044	.072	.239	.077	.036
Delta AM	.360*	.059	-.034	-.063	.284	.025	-.334	-.451 [†]	-.409	-.081	.653**	.500 [†]	.641**	.814**	.733**

Table 2.4. Correlations between wake EEG and NREM sleep EEG variables. [†] p≤.1, * p≤.05, ** p≤.01, *** p≤.001

Variables	Beta Activity			Alpha Activity			Delta Activity		
	B	SE	β	B	SE	β	B	SE	β
<i>EEG Wake</i>	2.000	.676	.443**	.036	.228	.033	.071	.370	.036
<i>EEG NREM Sleep</i>	1.519	.660	.345*	.242	.141	.354	.007	.029	.046
<i>F</i>	6.469***			2.342			.054		

Table 2.5. Multiple Linear Regression. DV = Positive VAS. * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

Variables	Beta Activity			Alpha Activity			Delta Activity		
	B	SE	β	B	SE	β	B	SE	β
<i>EEG Wake</i>	-2.071	.874	-.392*	-.026	.277	-.020	.031	.434	.013
<i>EEG NREM Sleep</i>	-1.239	.854	-.240	-.201	.172	-.251	-.001	.034	-.007
<i>F</i>	5.112**			1.078			.003		

Table 2.6. Multiple Linear Regression. DV = Negative VAS. * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

	Total Sample				Depressed Group				Healthy Control Group			
	VAS Positive	PANAS Positive	LOT	ER89	VAS Positive	PANAS Positive	LOT	ER89	VAS Positive	PANAS Positive	LOT	ER89
<i>Beta - Wake</i>	.459**	.360*	.217	.301 [†]	.609*	.433 [†]	.273	.262	.446 [†]	.505*	.319	.431 [†]
<i>Beta - Sleep NREM</i>	.461**	.376*	.305 [†]	.300 [†]	.195	.148	-.083	-.169	.552*	.351	.538*	.440 [†]

Table 2.7. Post-hoc correlations comparing the relationship between EEG and VAS to other measures approximating positive mood.

PANAS = Positive and Negative Affect Schedule

LOT = Life Orientation Test (measures optimism)

ER89 = Ego-Resilience Scale (measures psychological resilience)

[†]p≤.1, *p≤.05, **p≤.01

	Total Sample				Depressed Group				Healthy Control Group			
	VAS Negative	PANAS Negative	MASQ Anxious Arousal	MASQ Anhedonia	VAS Negative	PANAS Negative	MASQ Anxious Arousal	MASQ Anhedonia	VAS Negative	PANAS Negative	MASQ Anxious Arousal	MASQ Anhedonia
<i>Beta - Wake</i>	-.404*	-.003	-.021	-.130	-.546*	-.075	-.005	-.456 [†]	-.427 [†]	.458 [†]	.062	.082
<i>Beta - Sleep NREM</i>	-.343 [†]	-.091	-.052	-.307	-.179	.184	-.124	.207	-.321	-.193	.208	-.599*

Table 2.8. Post-hoc correlations comparing the relationship between beta activity and VAS to other measures approximating negative mood.

PANAS = Positive and Negative Affect Schedule

MASQ = Mood and Anxiety Symptom Questionnaire

[†]p≤.1, *p≤.05, **p≤.01

	Total Sample		Depression Group		Healthy Control Group	
	Sleep Quality	AM Restfulness	Sleep Quality	AM Restfulness	Sleep Quality	AM Restfulness
<i>Beta - Wake PM</i>	.405*	.352*	.266	.266	.338	.250
<i>Beta - Sleep NREM</i>	.142	.142	.130	.130	.158	.158

Table 2.9. Post-hoc correlations between beta activity with sleep quality and restfulness in the morning. † $p \leq .1$, * $p \leq .05$, ** $p \leq .01$

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CHAPTER 3

Faster Frequency Sleep qEEG Activity, Mood, and Depression

Introduction

Anecdotal and scientific evidence indicate that one's cognitive and emotional functioning can be compromised by poor sleep occurring the previous night (Pilcher & Huffcutt, 1996). Not surprisingly, sleep disturbances such as difficulty initiating/maintaining sleep, or restless sleep, are reported in almost all mental illnesses (Harvey, 2008). Sleep difficulties are especially relevant in major depressive disorder (MDD), with over 80% of patients with depression reporting poor quality sleep linked with adverse consequences for mood and daytime functioning (Reynolds & Kupfer, 1987). However, despite the general acknowledgement of the intimate relationship between sleep and depression, the precise mechanisms by which sleep affects mood dysregulation in depression still remains unclear.

While some research has established changes in sleep associated with depression, such efforts have been mostly confined to methods that are only descriptive of gross changes in the organization of sleep (i.e., sleep macroarchitecture). This approach is not without limitations (Armitage et al., 1995). Firstly, the process of quantifying sleep macroarchitecture relies on visual scoring of sleep stages, which assigns a single stage score to each 30 second epoch. This may not fully capture the range of bioelectrical information available. For example, signs of hyperarousal in the central nervous system (intrusions of fast frequency activity co-occurring with slow activity) may not be captured via stage score data, especially if the time spent in slow-wave sleep is similar to that of a well-functioning central nervous system. In short, the use of stage scores can be too reductionistic to describe more nuanced changes in encephalographic (EEG) activity. This loss of information may preclude discernment of mechanisms that contribute to poor sleep and its consequences. Secondly, evidence suggests

that sleep may not occur in these discreetly bounded stages (Armitage, Hoffmann, Loewy, & Moffitt, 1989), indicating a need for a more ecologically valid construct in understanding the relationship between sleep and affective disorders. Such limitations suggest that a more comprehensive approach may provide additional evidence that further informs the role of sleep in depression.

Alternatively, a quantitative EEG approach may be more descriptive of brain physiology via measures of EEG frequencies across the sleep stage domains (Armitage, Hudson, Trivedi, & Rush, 1995). This approach characterizes segments of EEG activity into subcomponents based on frequency bins, and therefore enables the quantification of slower versus faster frequency activity within the segment of EEG. This method is known as Power Spectral Analysis (PSA), and is based on Fast Fourier Transform (FFT) that allows for the digital production of data. Instead of assigning singular sleep stages (e.g. stages 1, 2, 3, 4, or REM) based on general and arbitrary criteria, PSA relies on mathematical algorithms to describe neurophysiology. It has been suggested that sleep in MDD can be disturbed for two reasons. Sleep in MDD may be disturbed due to a decrease in slow-wave activity that is indicative of restoration (Armitage, 2007; Borbély et al., 1984), or alternatively due to intrusions of fast-frequency (i.e., beta activity) that is indicative of hyperarousal (Armitage 1993; Nofzinger et al., 2000). Slow-wave activity has been associated with deeper quality sleep, and plays an important role in restoration on various levels, including synaptic homeostasis as well as metabolic regulation (for review, see Tononi & Cirelli, 2006). On the other hand, fast-frequency activity has commonly been associated with cortical arousal, especially during non-REM (NREM) sleep. Research in insomnia has posited that excess fast-frequency activity during sleep reflects hyperarousal of the central nervous system (Mendelson et al., 1986; Riemann et al., 2010; Stepanski et al., 1988), and therefore contributes to difficulties transitioning to and maintaining a sleep state. Due to the intimate relationship between insomnia and depression, it has also been proposed that hyperarousal may similarly explain poor quality sleep and its daytime consequences in depression (Armitage & Hoffmann, 1997; Wallace B. Mendelson et al., 1987; Nofzinger et al., 1999), especially in females (Armitage & Hoffmann, 2001; Roseanne Armitage et al., 1995).

It has also been proposed that depressed men and women may show differences in sleep. The distinction of sex differences is important because it may point to different etiologies or underlying mechanisms in the experience of depression, and therefore may require differences in intervention. Previous research has demonstrated that compared to women with MDD, men with MDD show significantly lower amounts slow-wave activity at the beginning of the night, and a slower rate of decay of slow-wave activity throughout the night (Armitage & Hoffmann, 2001). This suggests that the sleep neurophysiology of depression in men may be different from women, with men showing a tendency towards a less responsive sleep homeostatic system. Previous research has also proposed that hyperarousal may be more pronounced in women (Armitage et al., 1995). Together, these sex differences indicate that the way in which sleep abnormalities contribute to depression may involve disparate mechanisms, and may therefore respond differently to the interventions.

Additionally, while studies have sought to delineate ways in which sleep in depression differs from healthy individuals, few studies have explored how the documented abnormalities in sleep are related to mood and symptomatology in depression. As mentioned earlier, research examining group differences between depressed and healthy individuals discovered differences in slow-wave activity (for review, see Armitage & Hoffmann, 2001); however, few studies have examined how the decrement in slow-wave activity is related to mood and symptomatology in depression. Similarly, findings describing intrusions of fast-frequency activity has been posited to reflect hyperarousal in depression (Armitage & Hoffmann, 1997; Mendelson et al., 1987; Nofzinger et al., 1999), though the relationship between mood and depression symptoms with fast-frequency activity during sleep has been infrequently examined. Though there is relatively little work exploring how cortical activity during sleep relate to daytime mood in depression, studies conducted in healthy controls indicate that sleep is directly related to mood. For example, previous research have demonstrated that sleep loss affects one's experience of stress (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), and also disrupts one's ability to regulate negative affect (van der Helm & Walker, 2011). Together, the research suggests abnormal cortical activity in the fast and slow frequencies during sleep in depression may not only reflect

differences from healthy individuals, but also relate to the experience of stress and negative affect in depression.

In order to further delineate how sleep EEG influences depression, this study examines how quantitative EEG differs by depression diagnosis as well as gender. Differences were also subsequently related to depression symptoms, mood, and sleep quality. Given prior findings, it is hypothesized that mood, depressive symptoms, and sleep quality will either be predicted by either 1) a decrease of slow frequency activity (delta and theta bands), or 2) an increase of fast frequency activity (alpha, beta, and sigma bands). If hyperarousal were to be found, we would also expect to see increased hyperarousal in women compared to men.

Methods

Archival sleep data collected from the University of Texas Southwestern Medical School (UTSW) and University of Michigan (UM) were used in this present study. Analyses did not reveal any group differences by site of data collection¹. Data from participants in sleep studies between 1991 and 2011 were included in this sample. All participants were recruited for sleep studies through flyers posted in the community. Subjects all received a telephone screen, which was then followed with a Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID; American Psychiatric Association, 1994). The SCID for the DSM-III or DSM-IV was administered depending on date of recruitment. A detailed personal and family history was collected at the clinical interview. None of the participants were engaged in shift-work or reported independent sleep disorders (e.g., obstructive sleep apnea, narcolepsy, bruxism, and periodic limb movement disorder).

Once enrolled in the sleep study, all participants maintained a regular sleep schedule and recorded sleep diaries five days prior to the first night of the sleep study. Actigraphy data, based on physical movement and light exposure, was also collected to confirm the accuracy of the sleep diary records. All normal control participants were medically fit and had no personal or family history of Axis I disorders based on the SCID. Depressed participants were physically

¹ This analysis mirrored the main analysis in this manuscript, with site (UTSW, UM) as the between-groups factors. No significant interactions or main effect with site were detected.

healthy, but met DSM-III or DSM-IV criteria for a current major depressive episode without psychosis. Clinical interviews were conducted by doctoral level clinicians, clinically trained and supervised graduate students, and licensed and trained social workers. Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) scores were also completed in order to measure severity of depression symptoms. Eighty-two healthy controls and seventy-eight patients with MDD from the archival database were included in this analysis. Participants were selected randomly from all sleep studies which included depressed subjects between the ages of 18 and 45. Groups did not differ by sex (see Table 3.1).

Signal Processing

Participants' sleep EEG were recorded on either a four or eight EEG electrode montage, including leg leads, chest respiration band, and a nasal-oral thermistor. The eight EEG montage included electrodes at the left and right frontal, central, parietal, and occipital areas (F3, F4, C3, C4, P3, P4, O1, O2), whereas the four EEG montage included central and parietal areas (C3, C4, P3, P4). First night polysomnography recording was used to rule out any suspected sleep disordered breathing, periodic limb movements, bruxism, or other independent sleep disorders. Bipolar chin-cheek electromyograms (EMGs) were also recorded. EEG electrodes were referenced to the left and right ear lobes linked together through to a 10 kV resistor to minimize inhomogeneous current flow and potential artifactual hemispheric asymmetries (Nunez, 1981). EEG was transduced by GRASSTM P511 AC amplifiers set at a sensitivity of 5 (50 mV, 0.5 s calibration), corresponding to a gain of 50,000. The half-amp low- and high-band pass filters were set at 0.3 and 30 Hz, respectively. A 60 Hz notch filter was also used to attenuate electrical noise. Signals were digitized on-line at 250 Hz (62.5 Hz for electrooculogram and electromyogram) through a 16-bit MICROSTARTM analog-to-digital converter and displayed on a digital polygraph system designed and validated in over 500 subjects at UTSW. All raw digitized data were stored on mass media.

Behavioral Measures

All participants completed the HRSD, and a subset of depressed participants (N=36) also reported their mood following sleep via the Profile for Mood States questionnaire (POMS; McNair, Lorr, & Droppleman, 1971), as well as a Post-Sleep Questionnaire that measured perceived sleep onset latency, wake after sleep onset, time in bed, time asleep, as well as visual analogue scales rating the quality of sleep, restfulness upon awakening, and sleepiness upon awakening.

Data Analyses

Sleep was stage-scored on an epoch-by-epoch basis according to Rechtschaffen and Kales' (Rechtschaffen & Kales, 1968) criteria by trained technicians with 90% inter-rater reliability who were blind to the diagnostic status of the participants.

EEG power by hour of night was quantified across five frequencies using power spectral analysis (PSA), which generates numerical representations of discrete frequency events. PSA is based on the use of fast Fourier Transform (FFT; Gottman, 1981), which is a commonly used strategy for sleep EEG analysis (Campbell, 2009). FFT uses a mathematical algorithm to decompose time series data into discrete sine/cosine frequencies. In this study, FFTs were applied to 2 sec segments of EEG data. The resulting power values (power under the curve; expressed in μV^2) were then averaged within each epoch (30 seconds) in order to match conventions used in sleep stage scoring (Rechtschaffen & Kales, 1968). Only epochs from stage 1, 2, 3, 4, and REM were included for analysis. Summations of power across frequencies were produced for the following categories: delta (0.5 Hz to < 4 Hz), theta (4Hz to < 8Hz), alpha (8 Hz to < 12 Hz), sigma (12 Hz to < 16 Hz), and beta (16 Hz to < 32 Hz).

Because central electrodes were recorded in all participants, analyses were initially conducted using data from C3 and C4 in order to maximize sample size. The EEG data were submitted to a repeated-measures MANOVA, with Frequency (Delta, Theta, Alpha, Sigma, and Beta), Laterality (C3 and C4), Hour of sleep (hours 1 through 5), Sex (Male, Female) and Group (Healthy Control and MDD) as independent variables. Follow-up analyses were also conducted on a subset of participants for whom frontal electrodes were also recorded (N=110: MDD = 36, HC = 74). In order to further investigate the relationship between EEG characteristics and

depression severity, multiple linear regressions with HRSD scores entered as the dependent variable were completed in order to establish sleep EEG predictors of depression symptoms. Linear regressions were completed with both combined groups as well as separately to distinguish differences between groups. Finally, correlations between POMS subscales and sleep EEG variables were also conducted.

Results

Group differences

The five-way Frequency \times Laterality \times Hour of Sleep \times Sex \times Group indicated that differences in EEG power between groups varied by frequency and hour of sleep, Frequency \times Hour of Sleep \times Group, $F(16, 139)=2.986$, $p<.001$, with the MDD group showing significantly less power than HCs in the first hour of the night in the theta, $F(1,156)=12.327$, $p<.01$, and delta bands, $F(1,156)=20.439$, $p<.001$ (see Figure 3.1). Similarly, the MDD group also showed significantly less power compared to HCs in the last hour of the night in the theta, $F(1,154)=4.932$, $p<.05$, and delta bands, $F(1,154)=4.545$, $p<.05$. No group differences were detected in the beta frequency.

Overall, results show lower EEG power in the MDD group ($M = 126.492$, $SE = 2.868$) compared to the healthy control (HC) group ($M=135.872$, $SE=2.891$), Group, $F(1,154)=5.308$, $p<.05$. While not significant, the MDD group also exhibited lower EEG power across all frequencies in each remaining hour of the night (see Figure 3.2). Group differences did not vary by sex, though females across both groups showed higher overall EEG power compared to males, Sex, $F(1,154)=5.808$, $p<.05$ (see Figure 3.3). HCs, but not the MDD group, showed generally higher EEG power across frequencies in the right hemisphere compared to the left hemisphere, Laterality \times Group, $F(1,154)=7.141$, $p<.01$ (see Figure 3.4).

Post-hoc analyses conducted on the frontal electrodes also confirmed no group differences in the Beta frequency, Group, $F(1,81)=.437$, $p>.05$. Power analyses conducted using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) revealed adequate power (.8) to detect group differences. Marginal group effects were detected in the Alpha and Theta frequencies, with the MDD group also showing lower power, Alpha: Group, $F(1,106)=3.428$, $p<.10$, Theta:

Group, $F(1,106)=3.583$, $p<.10$. Results also confirmed lower power in the MDD group in the first hour of the night in the Alpha, $F(1,106)=5.314$, $p<.05$, Theta, $F(1,106)=7.773$, $p<.01$, and Delta frequencies, $F(1,106)=5.320$, $p<.05$.

Depression effects

In order to examine the relationship between EEG characteristics and depression severity, additional regression analyses were performed. Results revealed low frequency activity (delta and theta) during the first hour in both hemispheres significantly predicted HRSD scores, ($R^2=.142$, $F(2,159)=12.980$, $p<.001$). Decreased activity in the slow frequency band predicted increased HRSD scores on both the left ($\beta=-.250$, $p<.01$) and right hemispheres ($\beta=-.350$, $p<.001$). When both hemispheres were included simultaneously in the model, results also revealed a laterality effect with relative increased activity in the left hemisphere predictive of increased HRSD scores (see Table 3.2). Analyses repeated using EEG power across the night revealed the same patterns.

Results from the hierarchical regression also showed that, after entering low frequency activity in the first hour into the model, high frequency activity in the first hour (beta and sigma) predict additional significant variance in HRSD scores. Analyses also revealed that this relationship was moderated by sex (see Table 3.3). Post-hoc regressions indicated that high frequency activity best predicted HRSD scores in females (see Table 3.4). Analyses repeated using EEG power across the night also revealed the same patterns.

Mood effects (POMS and Post Sleep Questionnaire)

Correlations revealed that individuals with depression reporting higher Tension-Anxiety scores also exhibited decreased left and right side delta activity across the night (left: $r = -.424$, $p < .01$; right: $r = -.419$, $p < .05$), and decreased left side beta activity across the night ($r = -.382$, $p < .05$). Depression-Dejection scores showed a trend in the same direction, with decreased right delta activity across the night associated with increased low mood ($r = -.322$, $p = .05$). Similarly, depressed individuals showed higher Tension-Anxiety scores with lower overall EEG power ($r = -.366$, $p < .05$). Beta activity in the first hour of the night also exhibited a negative correlation with Tension-Anxiety scores (left: $r = -.422$, $p < .05$; right: $r = -.336$, $p < .05$). A

comparable relationship was detected with the Confusion-Bewilderment subscale, with depressed participants showing higher Confusion-Bewilderment scores with decrease left and right side delta activity across the night (left: $r = -.342, p < .05$; right: $r = -.359, p < .05$).

Results from the Post-Sleep Questionnaire also revealed that individuals with depression reported higher restfulness following sleep with overall increased slow frequency activity during sleep. Specifically, positive correlations were detected between restfulness upon awakening with left and right Theta activity across the night (left: $r = .392, p < .05$; right: $r = .407, p < .05$) and left and right Delta activity across the night (left: $r = .359, p < .05$; right: $r = .354, p < .05$). Additionally, increased left and right Beta activity across the night was associated with decreased sleepiness upon awakening (left: $r = -.307, p < .05$; right: $r = -.272, p < .05$).

Discussion

This study aimed to characterize sleep microarchitecture in depression, examined sex differences in sleep microarchitecture, and explored the relationship between sleep brain physiology with depression symptom and mood profiles. This research addresses a gap in depression research by connecting brain activity during sleep to mood and depression severity.

Results from this study indicate that depression may generally be characterized by decreased slow-wave activity during sleep, especially in the slow frequency bands. This finding is congruent with the hypothesis suggesting that depression is associated with a deficit in the regulation of sleep-wake dependent process (Process S), which is indexed by the amount of slow-wave activity, especially during the first half of the night. Reductions in delta and theta activity were most prominent in the first hour of the night, which is congruent with the period where more delta activity is expected. Correlations also indicate that decreased delta and theta power is associated with decreased restfulness upon awakening, further confirming that this deficit is associated with the experience of non-restorative sleep.

In general, the reduction in slow-wave activity in depression during sleep may represent a deficit in generating adequate sleep that is restorative. Tononi and Cirelli (2003, 2006) have proposed that the mechanism of restoration in slow-wave activity may be related to synaptic homeostasis that occurs during slow-wave activity during sleep. This hypothesis, with some

supporting evidence, suggests that during slow-wave activity, neurons that are strengthened through synaptic potentiation during wakefulness are progressively downscaled with each NREM period, effectively bringing the average synaptic weight to an appropriate baseline level (i.e., synaptic homeostasis). Neuronal benefits from synaptic homeostasis include reduced energy expenditure towards maintaining higher synaptic weight, and increased space for growth of new synapses. Both of these consequences benefit learning and memory, in addition to other functions. Conversely, disruptions to synaptic homeostasis result in inadequate synaptic downscaling, and synapses are therefore overloaded upon awakening. Consequences of synaptic overload include reductions in neuronal excitability, increased synaptic failure, and reduced plasticity. Not surprisingly, these neuronal consequences also map onto symptoms characteristic of depression, such as fatigue, anhedonia, impaired attention and concentration, and decreased motivation. Reduced neuronal plasticity may even contribute to ineffective or inefficient attempts at behavioral change. Results from this study lend support for this hypothesis, with evidence that decreased slow-wave activity (indicative of inadequate synaptic downscaling) is associated not only with reduced restfulness upon awakening, but also with increased negative mood and depression severity. Specifically, decreased slow-wave activity during sleep was correlated with increased feelings of dejection and depression, confusion and bewilderment, and tension and anxiety. Taken together, the results indicate that depression is better characterized by a brain deficit in homeostatic processes that enable adequate brain restoration.

Disruptions to synaptic homeostasis may also have cascading effects in further disrupting mechanisms of emotion regulation during wakefulness. Reduced synaptic homeostasis may result in reduced prefrontal activation that is sometimes observed in depression (Tononi & Cirelli, 2006). The functioning of the pre-frontal cortex (PFC) is of particular interest because of its role in regulating the limbic area, which is largely implicated in the processing of negative emotions. In fact, recent research has indicated that sleep loss impacts the functioning of the PFC, resulting in the disinhibition of the limbic region (Yoo et al., 2007). Specifically, Yoo and colleagues (2007) demonstrated that when sleep deprived individuals were shown negative stimuli, their brains exhibited exaggerated reactivity in the

amygdala connected with deficits in PFC functioning. This disruption to the cortico-limbic circuit may represent another consequence of inadequate sleep homeostasis that explains the vulnerability to the development or exacerbation of depression symptoms in individuals with sleep disturbances.

Furthermore, the disruption to brain restoration during sleep may also adversely impact the immediate function of offline emotion regulation during sleep. Consistent with synaptic downscaling, other studies have pointed to the role of sleep in pruning and consolidation of emotional memories (Walker & van der Helm, 2009). Specifically, Walker and colleagues (2009) have proposed that REM sleep may play a role in disentangling the affective tone from negative episodic memories, thereby facilitating offline emotion regulation. Research examining fear conditioning has corroborated this with evidence that sleep can facilitate offline fear extinction (Payne, Stickgold, Swanberg, & Kensinger, 2008). It is possible that ineffective synaptic downscaling during NREM sleep may also compromise brain functioning during REM sleep, further detracting from one's ability to regulate and resolve past negative events, and in turn perpetuate depression.

Another aim of this study was to explore the presence of hyperarousal in a large sample of depressed individuals. Previous research have posited that sleep difficulties in depression may be related intrusions of high frequency activity during sleep that may represent a hyperarousal of the central nervous system (e.g., Perlis, Merica, et al., 2001). However, this study did not find evidence for hyperarousal in sleep in depression. This is the largest sample of clinically-validated depressed participants that we are aware of where hyperarousal in sleep was directly examined. Contrary to the hyperarousal theory, results in this study suggested that increased beta activity during sleep is associated with decreased sleepiness in the morning, as well as decreased feelings of tensions and anxiety. This finding may seem initially unexpected given previous research in primary insomnia suggesting that increased fast-frequency activity may represent hyperarousal of the central nervous system, which in turn results in decreased quality sleep. However, a closer examination of the research examining hyperarousal in primary insomnia suggests that increased beta activity may be found predominantly during sleep onset, as well as during stage 1 and REM sleep periods (Perlis, Merica, et al., 2001), rather than during

non-REM sleep. Moreover, stage 1 and REM sleep states more closely resemble wake cortical activity, and therefore are more likely to include faster frequency activity. Furthermore, several studies comparing high frequency activity in sleep between individuals with primary insomnia versus sleep difficulties secondary to a psychiatric disorder found that elevated beta activity was specific to primary insomnia (Lamarche & Ogilvie, 1997; Nofzinger et al., 1999; Perlis, Kehr, et al., 2001). Taken together, the findings in this study may provide further confirmation that depression better characterized by deficits in producing adequate restorative sleep rather than hyperarousal.

Finally, another goal of this study was to also examine sex differences in sleep in depression. Results revealed that whereas both males and females show a decrease in slow frequency activity, only female participants exhibited additional fast frequency activity associated with increased depression severity. This is somewhat consistent with previous research showing increased incidence and amplitude of beta activity in a small sample of depressed females (Armitage, Hudson, Trivedi, & Rush, 1995), and further evinces differences in neurophysiology in depression between the sexes. This may also indicate considerations of sex differences in depression interventions, such as medications for mood management.

Conclusions

This study is one of few which examines sleep in depression using a quantitative EEG approach, and explores its relationship to depression symptoms and mood. Results suggest that sleep in depression may be characterized by an overall decrease in slow-wave activity, and is related to increased anxious and depression mood the following morning. The decrease in activity is more prominent in the slower frequencies, indicating that this may be related to a dysregulation of the wake-dependent process. Furthermore, sex differences were detected, with only females showing additional increases in high-frequency activity related to increased depression severity.

Appendix

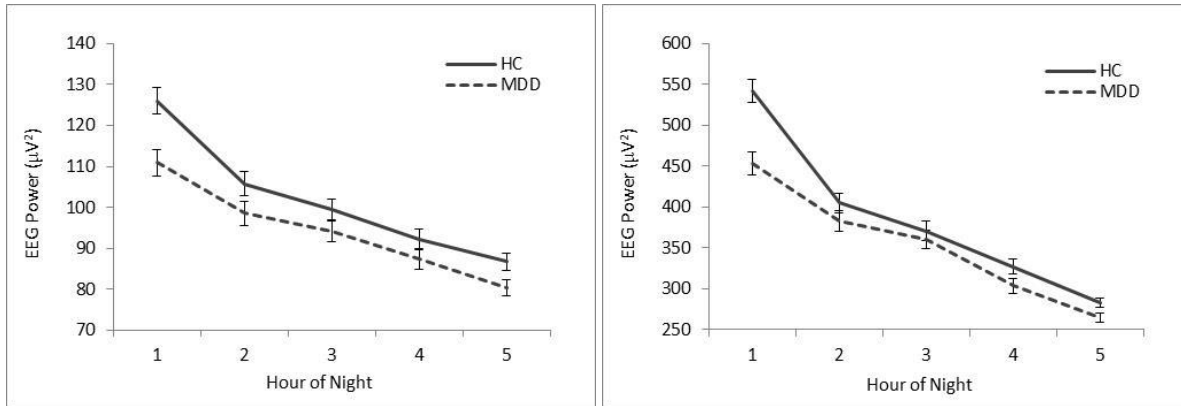


Figure 3.1. a) Theta power across the hours of the night. b) Delta power across the hours of the night.

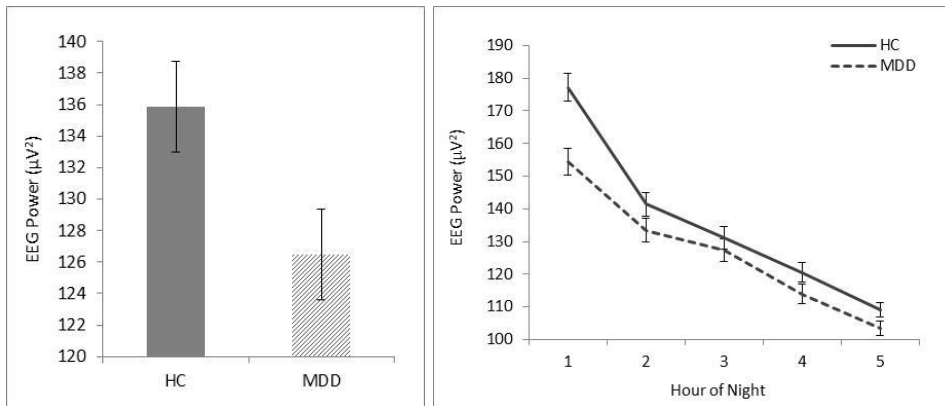


Figure 3.2. a) Average EEG power across the night. b) EEG power by hour across the night.

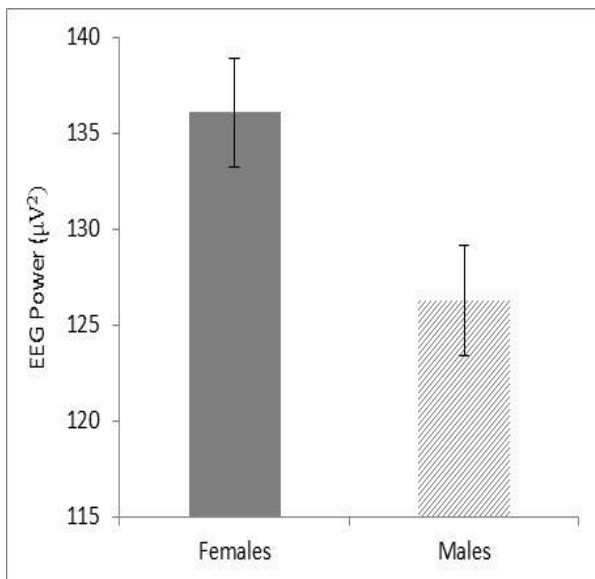


Figure 3.3. EEG power by sex.

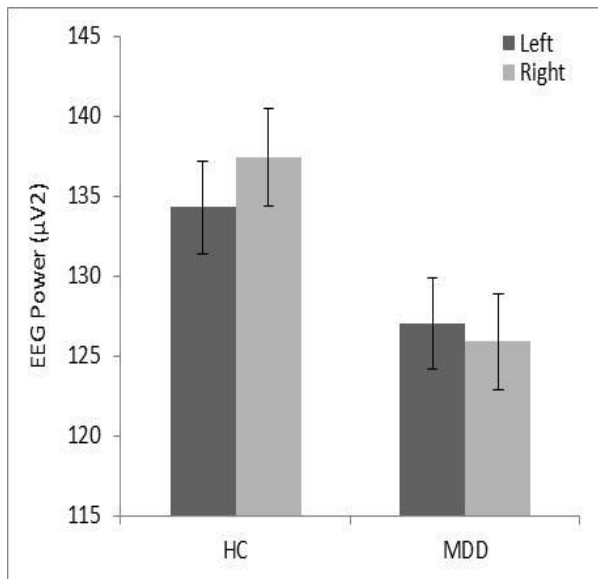


Figure 3.4. Right and left EEG power by group.

Variables	MDD (N=82)	HC (N=78)	p-value
Sex	47 ♀	36 ♀	ns
Age	30.6 (6.8)	28.6 (5.7)	ns
Hours in bed	6.8 (0.6)	6.9 (0.2)	ns
Sleep onset latency (min)	14.1 (13.2)	8.2 (11.1)	<.05

Table 3.1. Demographic and sleep variables.

Variables	B	SE	β
Hour 1: Right Slow Frequency	-.061	.016	-.907 ^{***}
Hour 1: Left Slow Frequency	.044	.017	.612 [*]
R^2	.142		
F	12.980 ^{***}		

Table 3.2. Summary of linear regression for variables predicting HRSD. * $p \leq .05$, ** $p < .01$, *** $p < .001$

Variables	Model 1			Model 2			Model 3			Model 4		
	B	SE	β	B	SE	β	B	SE	β	B	SE	β
Hour 1: Slow Frequency	-.021	.005	-.292 ^{***}	-.028	.006	-.403 ^{***}	-.029	.006	-.404 ^{***}	-.028	.006	-.402 ^{***}
Hour 1: Fast Frequency				.109	.041	.225 ^{**}	.093	.042	.193 [*]	.090	.042	.186 [*]
Sex							-3.316	1.703	-.148 [*]	-3.324	1.707	-.148 [*]
Sex \times Group										-.510	.845	-.045
R^2	.085			.113			.128			.125		
F	14.755 ^{***}			6.906 ^{**}			3.790 [*]			.364		

Table 3.3. Summary of hierarchical linear regression for variables predicting HRSD. * $p \leq .05$, ** $p < .01$, *** $p < .001$

Variables	Female			Males		
	B	SE	β	B	SE	B
Hour 1: Slow Frequency	-.034	.009	-.462 ^{***}	-.023	.008	-.341 ^{**}
Hour 1: Fast Frequency	.158	.054	.347 ^{**}	-.011	.067	-.020
R^2	.169			.123		
F	8.137 ^{***}			5.181 ^{**}		

Table 3.4. Summary of hierarchical linear regression split by sex for variables predicting HRSD. * $p \leq .05$, ** $p < .01$, *** $p < .001$

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CHAPTER 4

Resilience in Sleep and Depression

Introduction

Although sleep difficulty is a common symptom of major depressive disorder (MDD), research has indicated that sleep disturbance may also be etiologically related to the development and maintenance of MDD. For example, sleep disturbances such as chronic insufficient sleep, fragmented sleep due to noise, or a diagnosis of insomnia has been associated with increased risk for depression (Tkachenko et al., 2014), and even in predicting later onset of depression (Baglioni et al., 2011). Furthermore, previous research has also demonstrated reduction in depression symptoms when patients undergo cognitive behavioral therapy for insomnia (Manber et al., 2011).

One mechanism by which disturbances to sleep may increase risk for depression may be the affective consequences of sleep disruption (Baglioni, Spiegelhalder, Lombardo, & Riemann, 2010). Research indicates that individuals deprived of sleep demonstrate an exaggerated negative response to stressors (Yoo et al., 2007). Additionally, sleep deprived individuals also show a notable impairment in their ability to regulate negative emotions associated with stressors (van der Helm & Walker, 2011). Together, individuals who experience sleep disturbances may be left with higher levels of stress and impaired ability for emotion regulation, thereby increasing their risk for psychiatric difficulties. Though it is clear that sleep disruption can contribute to the development of depression, less work has been done in examining how the negative consequences of sleep disruption can be mitigated, especially for individuals already suffering from depression.

Although disturbances to sleep have direct negative consequences, some individuals appear less impacted by sleep loss than others. Recent studies examining these individual differences have identified certain characteristics, such as personality or genotype, that are associated with mood reactivity to sleep disruption (Rupp, Wesensten, Newman, & Balkin, 2013; Schröder, 2010). While personality and genetic makeup are among important factors in identifying individuals at higher risk of health complications from sleep disruption, these characteristics are not necessarily malleable, and therefore less amenable to interventions. Exploration of additional factors that may buffer against the negative impact of sleep disruption may allow us to identify ways of enhancing these factors that protect against subsequent negative consequences.

Psychological resilience may be a potential factor that buffers against the affective consequences of sleep disruption, and is also amenable to intervention. Psychological resilience is broadly characterized by an ability to respond and recover from environmental stressors (Block & Kremen, 1996; Lazarus, 1998), and buffers against potential threats to well-being (Khanlou & Wray, 2014). Research in resilience has employed a range of definitions; in this study, we conceptualize resilience as a trait that enables individuals to effectively engage in self-regulation following exposure to stressors, thereby resulting in less negative and more positive experiences and mood. Consistent with the definition advocated by Rutter (1987), resilience is defined not merely as the absence of mental illness, but instead how one responds to threat. As such, while depressed individuals on average may possess lower resilience, individuals with depression may still report varying levels of resilience that serve protective functions. This conceptualization is consistent with previous research demonstrating that combat veterans experiencing post-war depression show varying levels of severity corresponding to their level of resilience (Youssef et al., 2013). Furthermore, this conceptualization also allows for the possibility of strengths-based interventions that target the enhancement of existing resilience in depression.

Understanding the role of resilience in sleep may be particularly important because it has been established as a factor that can be targeted through interventions. For example, several studies have documented the efficacy of the Penn Resiliency Program, a group

intervention that teaches adolescents in school a variety of strategies to problem solve and cope with difficult social and emotional situations. This intervention has been shown to reduce the onset and severity of depression symptoms (Brunwasser, Gillham, & Kim, 2009), demonstrating that resilience is a modifiable trait via intervention. If psychological resilience has a role in protecting individuals from the affective consequences of sleep disruption, it may also have a cascading effect in preventing not only depression, but a myriad of physical and mental health complications.

Very few studies have examined the relationship between resilience and sleep in the context of psychopathology. Some nascent research has pointed to the role of resilience in protecting individuals from poor sleep and its adverse consequences. A recent study in adolescents examining “mental toughness”, a concept that overlaps with resilience, demonstrated that mentally tough adolescents exhibited better sleep indexed by higher sleep efficiency, less number of awakenings, less light sleep, and more deep sleep (Brand et al., 2014). Additionally, another recent correlational study in healthy children suggested that resilience mediated the relationship between reported sleep disturbance and externalizing and internalizing problems (Chatburn, Coussens, & Kohler, 2014). Taken together, there is strong evidence for resilience as a potential buffer against the negative consequences of sleep disruption. However, additionally work is needed in exploring the relationship between resilience and sleep in adults, especially those already struggling with mood disorders.

In order to address current gaps in the research, the present study sought to examine the role of resilience in the relationship between sleep and depression. Participants in this study completed an experimental protocol designed to compare mood responses between baseline sleep and disrupted sleep. By including both depression and psychological resilience as independent variables, this study can examine if mood responses to sleep disruption in depression versus healthy individuals is associated with lower psychological resilience. Specifically, this study tested if 1) resilience can serve as a buffer against the negative affective consequences of sleep disruption, and 2) if this buffering effect of resilience differs between depressed or healthy individuals. This study also tested if resilience in healthy individuals is related to better quality sleep, indexed by less difficulties falling and staying asleep, in addition

to deeper quality sleep. It was hypothesized that depressed individuals would exhibit more negative mood and less positive mood in response to sleep disruption compared to healthy individuals. It was also hypothesized that individuals reporting higher resilience will show attenuated disruptions to mood following interrupted sleep. Finally, if depressed individuals lacked resilience, results should reveal a differential effect of resilience between healthy and depressed participants. Contrastingly, if resilience serves as a buffer for both depressed and healthy individuals, the attenuation of mood disruptions should not differ by diagnosis.

Methods

Participants²

A total of 34 participants (19 females) between the ages of 18 and 50 years old were recruited from the community via fliers and included in this study. Eighteen of these participants were healthy controls with no psychiatric history, do not meet diagnostic criteria for any Axis I disorder, and scored score of less than seven on the Beck Depression Inventory II (BDI-II). Sixteen of these participants were individuals who meet criteria for Major Depressive Episode based on DSM-IV-TR criteria, with a BDI-II score of 14 or higher. Procedures and recruitment for this study complied with the ethical standards of the Institutional Review Board.

Participants in this study were recruited as part of a larger study investigating the cognitive consequences of sleep disturbance in depression. Exclusionary criteria in this study included history of head injury resulting in loss of consciousness longer than 2 minutes, neurological diseases, use of psychotropic medications, and co-occurrence of independent sleep disorders (e.g., obstructive sleep apnea, narcolepsy, restless leg syndrome, bruxism). Participants were also excluded for lifetime histories of substance dependence, bipolar I or II disorder, psychosis, and anorexia or bulimia. Participants received \$10 for each hour of screening, and \$75 for each night of research participation.

² This study was part of the same protocol as in study 1, and the data is therefore collected from the same sample as study 1.

Experimental Conditions

Each participant completed two nights (adaptation, baseline) with acquisition of polysomnography. Prior to the first night, participants were asked to maintain five nights of a regular sleep schedule consistent with the sleep schedule during the study. Sleep schedules were approximated to the participants' natural sleep schedule at the time of recruitment. Compliance with the schedule was monitored through sleep diary and actigraphy (measurement of light and motion). Any deviations from their designated schedule that were greater than 2 hours prior to their first night were grounds for study exclusion. Additionally, participants were asked to refrain from use of caffeine after 12 noon, and abstain from alcohol or drug use. This pre-study period was followed by three consecutive nights in the sleep laboratory, with the first night serving as adaptation to the new sleep environment and as a screening for independent sleep disorders.

Slow Wave Activity (SWA) Interruption.

All participants completed an interruption night, during which their slow-wave activity was interrupted using tones delivered via earphones. Slow-wave activity is associated with deeper and more restorative sleep, and has also been associated with daytime mood. The delivery of tones maximized disruption to slow-wave activity without waking the subject. Slow-wave activity (delta waves) was visually detected throughout the night. Upon detection of two consecutive delta waves, 1000 Hz tones ranging from 20-100 dBs were played at 15 second intervals increasing by 5 dBs until signs of interruption is seen (i.e., movement or arousal, increased muscle tone, increased fast frequency activity, sleep stage shift, EEG desynchronization, alpha burst, and/or slow eye movements).

Measures

Psychological resilience in this study was captured using the Ego-Resiliency Scale (ER89; Block & Kremen, 1996). The ER89 consists of 14 items measuring the ability to return to an individual's baseline level of ego-control following temporary environmental changes or stresses. Participants rate each item on a 4-point likert scale ranging from 1 (Does not apply at

all) to 4 (Applies very strongly). Items include response to stressors (e.g., “I quickly get over and recover from being startled”, “I get over my anger at someone reasonably quickly”), as well as the anticipation of positive experiences in situations containing risk (e.g., “I enjoy dealing with new and unusual situations”, and “I enjoy trying new foods I have never tasted before”). Block and Kremen (1996) reported high reliability, with a coefficient alpha of .76 at both ages 18 and 23 in that sample. Additionally, high correlations of ER89 score across 5 years have been reported with coefficients of .67 and .51 for females and males after adjusting for attenuation. Windle, Bennett, and Noyes (2011) also reported rating high construct validity of the ER89 among nineteen other resiliency scales.

Depression severity was measured via a version of the Beck Depression Inventory (BDI-II) modified to assess current symptoms instead of symptoms within the last two weeks. Mood was measured through Visual Analogue Scales (VAS), including both positive and negative mood items. The VAS was completed before and after sleep on baseline and interruption nights. For ease of interpretation, some analyses also used difference scores calculated for positive and negative mood between baseline and interruption nights to measure change in mood following SWA interruption.

Data Analysis

In order to test the relationship between resilience, mood after SWA interruption, and depression, a general linear model was conducted with scores on the VAS submitted as the dependent variable. Four independent variables were used, consisting of Valence (Positive Mod, Negative Mood), Night (Baseline, Interruption), Group (MDD, HC), and Resilience (ER89 scores). Data analyses first examined the affective consequences of slow-wave activity disruption between groups via the Valence × Night × Group interaction. Next, analyses tested the model predicting a buffering effect of resilience on mood consequences of SWA interruption by examining the Valence × Night × Resilience interaction. Finally, the Valence × Night × Group × Resilience interaction was tested to examine if the buffering effect of resilience on mood following SWA interruption was moderated by group.

Additionally, post-hoc analyses were conducted to compare the relative contribution of resilience versus depression in predicting changes in mood following SWA interruption. For ease of interpretation, difference scores on positive and negative mood taken between Baseline and Interruption night was used as the dependent variable. To examine the relationship between resilience, depression, and response to SWA interruption, correlations were conducted between the respective variables. Two hierarchical linear regressions were also conducted to examine resilience and depression severity as predictors of change in positive and negative mood following SWA interruption.

Finally, correlations were conducted between mood, resilience, and polysomnography variables on baseline night that were indicators of sleep quality, including ability to fall or stay asleep (sleep onset latency, early morning awakenings), restfulness of sleep (number of arousals across the night), and depth of sleep (percentage of N1 versus N3 sleep). It was hypothesized that better quality sleep in healthy controls would be related to positive mood consequences as well as resilience. No hypotheses were generated for the depressed group due to lack of previous research examining resilience and sleep in depression.

Results

Descriptive

Sleep characteristics were examined via polysomnographic variables and compared between the two groups via independent one-way ANOVAs (see Table 2.1). Results showed a difference in REM latency that was approaching statistical significance, with the MDD group demonstrating a shorter latency to REM sleep, as is consistent with the literature.

A manipulation check was also completed to examine the effectiveness of the SWA interruption condition. The SWA interruption protocol targeted the interruption of delta, which should subsequently result in less time spent in slow-wave sleep (N3 sleep). Means revealed approximately a 50% reduction in N3 sleep between baseline night (mean = 67.52, SD = 29.11) and SWA interruption night (mean = 33.32, SD = 33.31), with a paired sample t-test confirming statistical significance of this difference, $t(30)=8.292$, $p < .001$. Calculation of the effect size using Cohen's d revealed a value of 1.1, indicating a large effect size.

Sleep interruption and resilience

Result from the first analysis examining consequences of mood following SWA interruption revealed differential responses between HC and MDD groups on both positive and negative mood, Valence \times Night \times Group, Wald $\chi^2 = 11.677$, $p < .001$, with the MDD group showing more negative affective consequences following SWA interruption. Specifically, the MDD group showed significantly higher negative mood following interruption night compared to baseline night, whereas the HC showed no change in negative mood, Night \times Group, Wald $\chi^2 = 6.660$, $p < .01$. Furthermore, while the MDD group showed marginal decreases in positive mood following interruption night compared to baseline night, the HC group show significant increases in positive mood, Night \times Group, Wald $\chi^2 = 8.964$, $p < .01$ (see Figure 4.1).

The second analysis examined if resilience moderated affective consequences of SWA interruption. Results demonstrated that resilience buffered against the negative consequences of sleep interruption, Night \times Valence \times Resilience, Wald $\chi^2 = 23.021$, $p < .001$. For ease of interpretation, this was followed-up with correlations using change scores for positive and negative mood between nights. Results indicate that higher resilience is related to less negative mood and more positive mood following SWA interruption relative to baseline night (see Table 4.1).

The third analysis tested whether a diagnosis of depression moderated the buffering effect of resilience. Results did not show a significant Valence \times Night \times Group \times Resilience interaction, indicating that resilience did not differentially influence mood between MDD and HC groups following SWA interruption. Post-hoc analyses further revealed that change in positive and negative mood was significantly moderated by resilience for both MDD, Valence \times Night \times Resilience, Wald $\chi^2 = 8.930$, $p < .01$, and HC groups, Valence \times Night \times Resilience, Wald $\chi^2 = 16.944$, $p < .001$. In both groups, individuals with higher resilience showed less increases in negative mood and less decreases in positive mood following SWA interruption (see Figure 4.2 and Figure 4.3).

Resilience versus Depression

Post-hoc analyses were also conducted to examine the relative importance of resilience versus depression severity in predicting mood response to SWA interruption. For ease of interpretation, separate analyses were conducted using change scores as the dependent variable in two hierarchical linear regressions. Scores from the BDI-II were entered in the first model to test the significance of depression severity in predicting response to SWA interruption. The second model included scores from the ER89 in order to test whether resilience accounts for additional variance beyond depression severity.

Results revealed that depression severity did not significantly predict change in positive or negative mood following SWA interruption. In contrast, resilience was a significant predictor of change in positive and negative mood following SWA interruption, even after accounting for depression severity (see **Error! Reference source not found.** and **Error! Reference source not found.**).

Correlations

Correlations were also conducted in order to examine the relationship between resilience, mood, and sleep. Analyses were conducted separately for HC and MDD groups for a few reasons. Firstly, separating analyses by group may prevent illusory correlations that occur in the total sample that are driven by general group differences. Secondly, a hypothesis was only generated for the healthy control group, and not for the depressed group due to lack of previous research examining resilience and sleep in depressed adults. Finally, differences in sleep architecture have been documented in depression, which may mean that the relationship between resilience and sleep in healthy and depressed individuals may differ based on the changes in sleep architecture.

Consistent with our hypothesis, results in the HC group suggest that higher resilience is associated with better quality sleep. Specifically, higher resilience was significantly related to decreased stage 1 sleep and decreased early morning awakenings. Resilience was also significantly related higher positive mood ($r = .680, p < .01$), and lower negative mood ($r = -.578, p < .05$).

Correlations completed within the MDD group revealed increased negative mood with increased early morning awakening. Early morning awakening was also marginally related with decreased positive mood. No significant correlations were detected in the MDD group between sleep variables and resilience. Correlations between resilience with positive ($r = .366$) and negative ($r = -.284$) mood did not reach statistical significance, though they were in consistent directions with corresponding correlations in the HC group. Pearson correlation coefficients indicate medium effect sizes that would likely reach significance with increased sample size.

Discussion

This study examined the relationship between resilience and sleep by testing if resilience buffered against negative affective responses to sleep disruption in depressed and healthy individuals. Results indicate that psychological resilience does buffer against increases in negative mood and decreases in positive mood following interrupted sleep. Most notably, despite being generally more prone to mood disturbances after sleep interruption, depressed individuals reporting higher resilience also appear to benefit from the buffer against mood disturbances following interrupted sleep. This suggests that resilience not only benefits healthy individuals, but can also benefit those who are depressed. Furthermore, results suggest that there may be room for a strengths-based model of intervention even in individuals who already suffer from depression.

Results also suggest that, compared to depression severity, an individual's resilience may be more powerful in predicting mood responses to sleep interruption. This result adds a new dimension to previous research implicating interrupted sleep as a vulnerability factor to depression. Specifically, this study suggests that psychological resilience can serve to protect against the mental health risks of interrupted sleep. While ample evidence has implicated sleep as a risk factor for depression, sleep disturbance is considered a transdiagnostic process that impacts several forms of psychopathology (Harvey, Murray, Chandler, & Soehner, 2011). This further increases the potential impact of these results, and future research should explore how increasing resilience may reduce the negative consequences of sleep disruption.

As expected, results from this study demonstrated that when accounting for resilience, depressed individuals may be at elevated risk for negative emotional consequences of sleep disruption than healthy individuals. Specifically, disruptions to slow-wave activity appears to impact negative mood, which is consistent with other research showing baseline decreases in slow-wave activity in depressed individuals is related to increased depressed mood and symptom severity (see CHAPTER 3). When accounting for resilience, healthy individuals did not appear to experience an increase in negative mood, and interestingly showed an increase in positive mood after sleep interruption. While this is somewhat counterintuitive, one explanation may be based in research indicating that sleep deprivation disrupts the inhibitory pathway between the prefrontal cortex and the limbic region of the brain (van der Helm & Walker, 2011), which is largely implicated in processing of emotional information. This disruption of inhibition leads to hyperactivity in the amygdala, translating to increased intensity of emotions. Based on this evidence, it is possible that healthy individuals in this sample experienced an increase in intensity of their baseline positive emotions, and may similarly exhibit an exaggerated response if stressors were to be encountered. Given the smaller sample size in this study, this interpretation is tentative and would require further replication with a larger sample.

Results of this study may also have implications beyond depression. While reduction of sleep disturbances is ideal for health outcomes, there are certain circumstances where reducing disturbances to sleep may be difficult to achieve. Examples include disturbances to sleep due to environmental noise, such as nighttime road, rail, and air traffic. In fact, a recent review published by the National Institute of Environmental Health Sciences presented noise pollution as a public health concern, stating that nearly 100 million people in the United States (approximately 50% of the population) are at risk for health complications due to environmental noise exposure (Hammer, Swinburn, & Neitzel, 2014). Additionally, several studies have documented adverse effects of environmental noise on sleep (Basner, Müller, & Elmenhorst, 2011; Halonen et al., 2012; Smith, Croy, Ögren, & Waye, 2013) which are often challenging and cost-prohibitive to reduce. Furthermore, another recent study also documented that among individuals who are exposure to noise pollution, those who report

sleep disturbances were more vulnerable to mental health difficulties. Taken together, results from this study indicate that interventions to enhance resilience may also be considered as part of a larger solution to protect vulnerable individuals from the negative consequences of sleep disturbance.

Finally, as expected, results from this study also demonstrated that in individuals without psychopathology, higher resilience is related to better quality sleep, indexed by less time spent in lighter sleep and less fragmentation of sleep. This further confirms that sleep and mental health are intimately connected, and also provides evidence for sleep in not only reducing or preventing negative consequences, but perhaps also supporting or enhancing quality of life. This is particularly important because evidence indicates wide prevalence of insufficient sleep, with as high as 41.3% of individuals reporting insufficient sleep within the last 13 days (CDC, 2009).

Limitations

Limitations of this study include the smaller sample size, which may be limiting the detection of additional group differences in baseline sleep variables. Another limitation includes the self-report of resilience, which may be measuring an individual's self-efficacy around stress management. Future studies may include performance measures that index response and recovery from stress.

Conclusions

This study was aimed at exploring the relationship between resilience and sleep in depression as compared to healthy controls. Results indicate that even in depression, resilience can serve as a buffer against the negative mood consequences of sleep interruption. In individuals without psychopathology, resilience is related to less disturbed sleep. Future studies should aim to further delineate the relationship between resilience and sleep through more objective measures of resilience.

Appendix

	HC			MDD			Total Sample		
	ER89	VAS Negative	VAS Positive	ER89	VAS Negative	VAS Positive	ER89	VAS Negative	VAS Positive
<i>Sleep Onset Latency</i>	.305	.181	-.025	-.223	.130	.170	-.123	.257	-.201
<i>Number of Arousals</i>	-.174	-.139	.200	-.114	-.197	.346	.042	-.146	.171
<i>Early Morning Awakening</i>	-.617*	.061	-.561*	-.266	.533*	-.469 [†]	-.247	.004	-.292
<i>Percentage of N1</i>	-.553*	.373	-.519*	.395	-.304	.298	-.041	-.013	-.090
<i>Percentage of N3</i>	.163	-.252	.186	-.079	.152	-.167	-.049	.007	-.015

Table 4.1. Correlations (pearson's r) between resilience, mood, and sleep variables on Baseline night. [†] $p < .1$, * $p < .05$

	Total Sample		MDD		HC	
	ER89	BDI-II	ER89	BDI-II	ER89	BDI-II
Δ Positive VAS	.414*	-.080	.480 [†]	.031	.645**	-.384
Δ Negative VAS	-.356*	.127	-.649**	.201	-.364	.302

Table 4.2. Correlations (pearson's r) between resilience, depression severity, and changes in mood following SWA interruption. [†] $p < .1$, * $p < .05$, ** $p < .01$

	Model 1			Model 2		
	B	SE	β	B	SE	β
BDI-II	.137	.217	.113	-.196	.258	-.161
ER89				-.748	.350	-.453*
R ² (R ² Change)	.013			.143* (.131)		

Table 4.3. Depression severity and resilience as predictors of change in negative mood following SWA interruption. Dependent Variable: Δ Negative VAS (Bsl – Int). * $p < .05$, ** $p < .01$

	Model 1			Model 2		
	B	SE	β	B	SE	β
BDI-II	-.059	.190	-.056	.322	.213	.304
ER89				.856	.288	.597**
R ² (R ² Change)	.003			.230* (.227)		

Table 4.4. Depression severity and resilience as predictors of change in positive mood following SWA interruption. Dependent Variable: Δ Positive VAS (Bsl – Int). * $p < .05$, ** $p < .01$

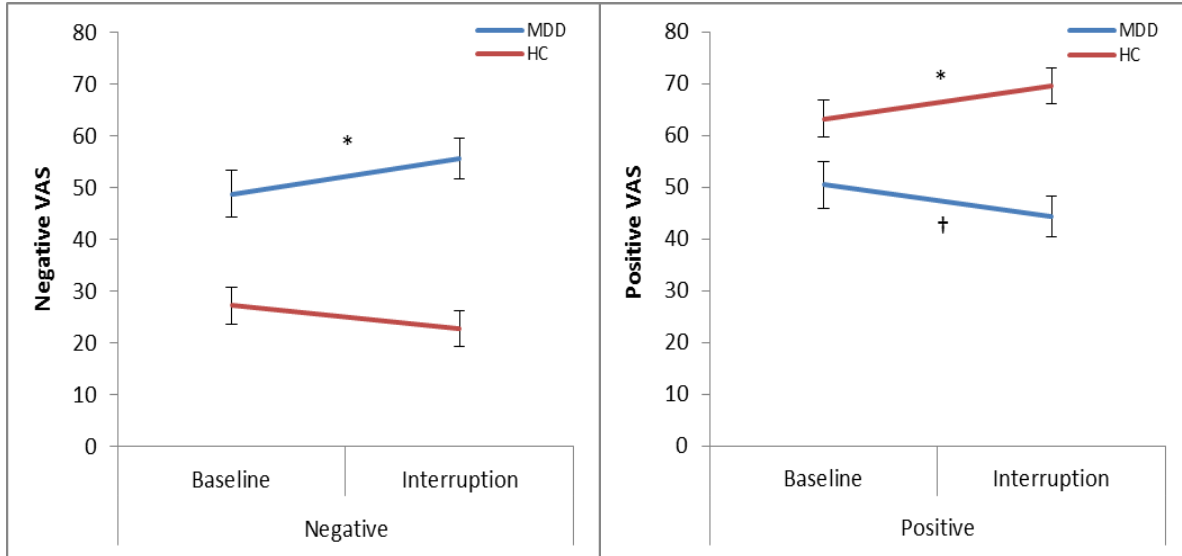


Figure 4.1. Change in negative and positive mood following SWA interruption night compared to baseline night. † $p < .1$, * $p < .05$

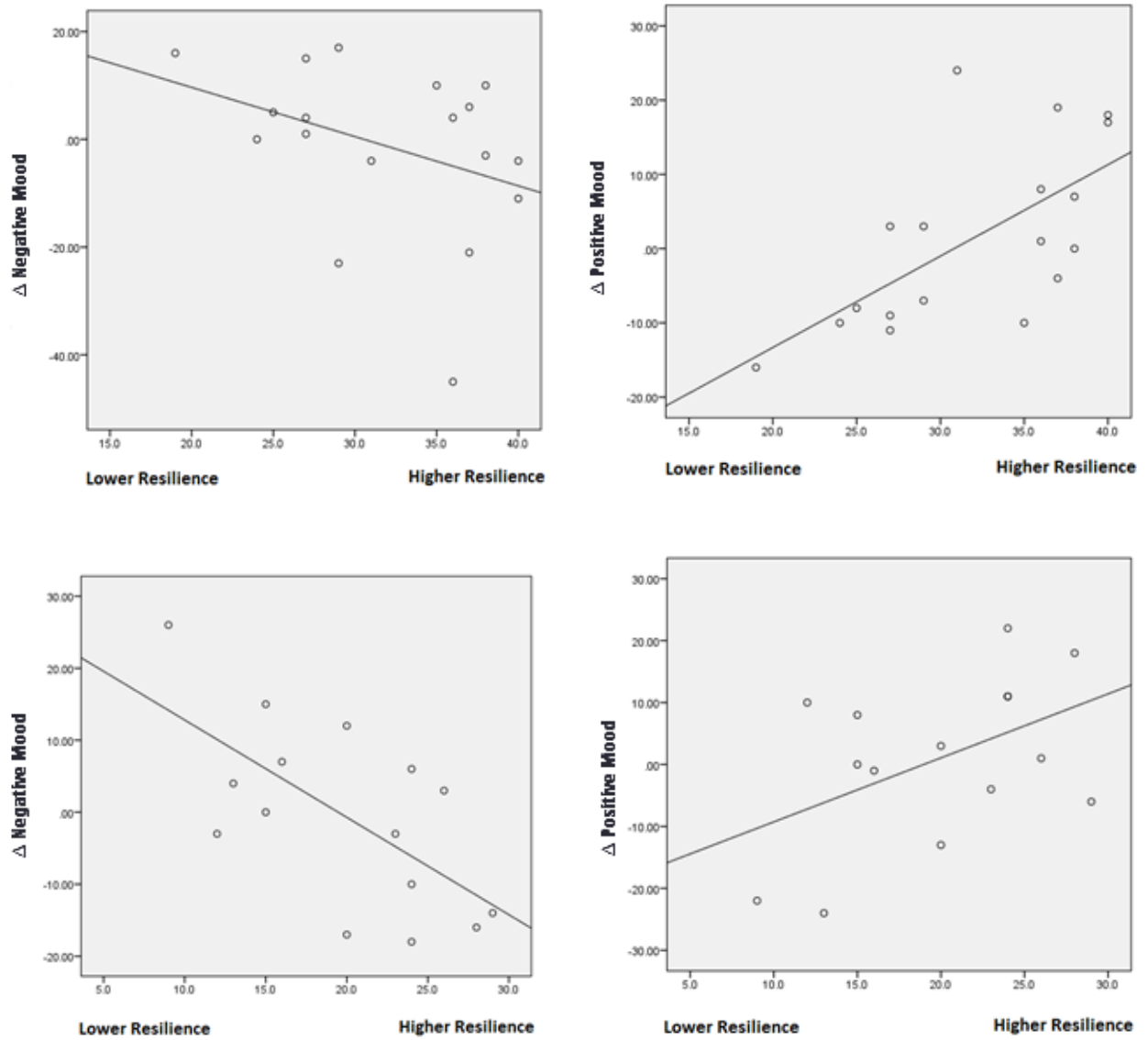


Figure 4.3. Buffer effect of resilience on change in negative and positive mood following SWA interruption in the MDD group.

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CHAPTER 5

General Conclusion

This dissertation addresses important disconnects in the literature of affective neuroscience in depression by bridging brain physiology between wakefulness and sleep. Sleep is of particular importance in depression not only because it is part of the symptomatology, but also because a plethora of evidence points of sleep physiology as a mechanism in the etiology of depression. However, despite evidence for the intimate relationship between sleep and depression, few studies have directly compared brain physiology across states of wakefulness and sleep, and how the physiology relates to the symptoms and experience of depression. Thus, the first study in this dissertation measured brain physiology during both resting wakefulness and sleep, and explored what aspects of cortical activity related to positive and negative mood in depression. Secondly, sleep research in depression have proposed two hypotheses regarding alterations in sleep. The first hypothesis posits that depression is characterized by deficits in the recovery functions of sleep, as indexed by reduced slow-wave activity. The second hypothesis posits that sleep in depression is characterized by hyperarousal in the central nervous system, leading to poor quality sleep as indexed by intrusions of fast-frequency activity. Thus, the second study in this dissertation directly examined both slow-wave and fast-frequency activity in depression, and explored how each related to depression severity and mood. Finally, while nascent research has begun to examine the role of sleep in promoting human flourishing and resilience, few studies have investigated this relationship in depression. Psychological resilience is particularly important to examine because it may be the first protective factor against sleep disruption that may be amenable as a treatment target. Thus, the third study examined the relationship between resilience and sleep, and if resilience can protect against the negative affective consequences of sleep disruption, even in individuals who already suffer from depression.

The first study demonstrated that increased baseline cortical arousal is associated with positive affective experiences. Both the healthy control and depressed group exhibited higher positive and lower negative mood with increased beta activity, which is indicative of cognitive activity. Results also show that decreased beta activity was associated with higher anhedonia in the depressed group, and higher negative mood on the PANAS (consisting of more high arousal negative affect items) in the healthy control group. Together, results in this study are consistent with previous research showing that higher baseline cortical activity is related to response to brief cognitive intervention (Deldin & Chiu, 2005). Results also provide further preliminary evidence that the decrease in cortical activity may be related to a lack of cognitive and emotional resources. This decrease may manifest as the experience of negative low arousal states, such as anhedonia and decreased motivation. Future studies replicating this result in a larger sample size will be necessary in order to maximize generalizability to the larger population.

The second study examined sleep in depression using a quantitative EEG approach, and explored its relationship to depression symptoms and mood. This study addressed the limitation of sample size in the first study by employing a much larger sample of depressed participants, though wake EEG was not available for investigation. Results suggested that sleep in depression may be better characterized by a brain deficit in generating adequate deep and restorative sleep, rather than a general intrusion of fast frequency activity. In fact, as found in the first study, decreased cortical activity during sleep was related to increased anxious and depressed mood the following morning. Results further confirm that depression is related to a dysregulation of the sleep-dependent process. However, sex differences were also detected, with only females showing additional increases in high-frequency activity related to increased depression severity.

The last study investigated the influence of resilience in the emotional consequences of sleep disruption in depression as compared to healthy controls. Results indicate that even in depression, resilience can serve as a buffer against the negative mood consequences to sleep interruption. In healthy individuals, resilience was related to less disturbed sleep, suggesting

that individuals with higher psychological resilience may possess a sleep system that is more robust, and therefore more able to respond to stress.

Together, this dissertation provides new insights and clarifications into the role of sleep in depression. Results indicate that not only is sleep different in depression compared to healthy controls, these differences are related to the both the symptom severity as well as mood. Furthermore, results also clarified that sleep in depression may be better characterized by a decreased in slow-wave activity rather than an intrusion of fast-frequency activity, though there appears to be a sex difference with females showing both decreased slow-wave activity and fast-frequency activity.

Decreased cortical activity during sleep, especially in the delta frequency as found in the second study, may represent disruptions in the recovery processes of sleep. One mechanism of sleep-dependent recovery may be the process of synaptic homeostasis. Synaptic homeostasis has been proposed to occur during slow-wave activity, and downscales synaptic strength that has been building during long-term potentiation (i.e., information processing and learning) across wakefulness (Tononi & Cirelli, 2006). Inadequate synaptic downscaling subsequently leads to synaptic overload, and therefore reduced neuronal excitability and increased synaptic failure during wakefulness. These neuronal consequences may explain characteristic symptoms of depression, such as fatigue, anhedonia, impaired attention and concentration, and decreased motivation, as suggested in the results of study two.

Deficiencies in slow-wave activity in depression may lead to a multitude of consequences. Firstly, inadequate synaptic downscaling during sleep likely results in impaired neuronal functioning during the following day (e.g., reduced neuronal excitability, increased synaptic failure), which may be experienced as decreased cognitive activity. As found in study one, decreased cognitive activity in depression is subsequently associated with poor mood consequences, which is consistent with previous research demonstrating that baseline cortical activity was found to predict mood reactivity to a brief intervention (Deldin & Chiu, 2005). Furthermore, results also provide further evidence that decreased cognitive activity may be particularly related with negative low arousal states, such as depressed mood and anhedonia. Together, these results suggest that reduced cortical activity may be an alternative biomarker

for depressive disorders marked by “negative” symptoms (i.e., anhedonia, decreased motivation, lethargy), and further proposes that this may be a consequence of a deficient sleep-dependent recovery process. In fact, symptoms marked by low arousal and low valence would be a natural consequence to inadequate restoration during sleep.

Consequential decreased cortical activity from non-restorative sleep may not only affect baseline mood states, but also extend to the individual’s ability to effectively engage in their environment. When non-restored neurons are less excitable, or even experience synaptic failures, it may restrict the amount of cognitive and emotional resources that is available to the individual. One instance of a resource or skill of particular importance is emotion regulation. Previous studies have already identified altered functioning of the prefrontal cortex (PFC), which plays a role in regulation of the limbic system. In fact, individuals who are deprived of sleep, and therefore deprived of synaptic restoration, are less able to regulate amygdala activity, resulting in exaggerated amygdala responses to stress (Yoo et al., 2007). Additionally, impairments in cognitive functioning have been well documented as consequences to sleep disruption (for review, see Durmer & Dinges, 2005). Together, this indicates that deficits in sleep-dependent restoration not only alters baseline mood, but also further increases reactivity to stress, paired with reduced cognitive resources to regulate the stress response. Moreover, the resulting state of increased stress may further disrupt sleep, thereby perpetuating the vicious cycle of depression.

Secondly, disruptions to sleep may also exacerbate depression by adversely impacting offline emotion regulation. An emerging body of research has begun exploring the role of sleep in offline emotion processing and emotion regulation (Walker & van der Helm, 2009). Though some of this nascent research has been focused on REM sleep, it is also possible that disruptions to NREM sleep can also have negative consequences in offline affect regulation, especially given the role NREM sleep in physiological restoration (Saper, Cano, & Scammell, 2005). This may also explain the relationship between reduced slow-wave activity in depression and poor mood. Unlike healthy sleepers who have the opportunity to effectively disentangle affect from negative episodic memories, depressed individuals may be deprived of this process and therefore wakeup with lingering negative affect from recent negative experiences.

Thirdly, the consequences of decreased slow-wave activity in depression may also impede responses to intervention. In fact, Tononi and Cirelli (2006) have indicated that disruptions to synaptic homeostasis reduces brain plasticity, which has been identified as a predictor of response to antidepressant treatment (Castrén & Hen, 2013). Engaging in change behaviors with reduced brain plasticity may also require increased effort and duration of practice in implementing behavioral change, which may lead to higher frustration, hopelessness, and therefore treatment attrition. Similarly, reductions in neuronal responsiveness as a consequence of decreased slow-wave activity may reduce effective engagement in pleasurable activities or meaningful experiences, and thus attenuate the effectiveness of interventions such as behavioral activation. Together, these results suggests that a brain deficit in generating adequate deep and restorative sleep may contribute to depression by disrupting baseline mood, interfering with neural mechanisms of emotion regulation, and mitigating responses to interventions.

Finally, this dissertation is also among the first studies to examine psychological resilience and sleep in depression via objective measures of sleep in depression. The relationship between sleep and positive mental health is fairly new, and most existing research has focused on subjective reports of sleep quality as dependent variables. This dissertation provides evidence that psychological resilience in healthy controls is related to fewer disruptions to sleep, suggesting that sleep may also serve as a protective factor in mental health. Results also reveal that both healthy controls and depressed individuals reporting higher psychological resilience benefit from the buffering effect of resilience against the negative affective consequences of sleep disruption. Furthermore, in predicting change in mood following sleep disruption, psychological resilience appears to be a more powerful predictor than depression severity. Together, these results indicate that even though sleep disruption is a powerful risk factor for depression, psychological resilience may be influential in reducing this risk.

Results from the third study shows promise in further delineation of the important and yet poorly understood role of resilience and sleep in depression. While this study presumes resilience as a stable characteristic that is related to sleep quality, it is also possible that changes in sleep quality may impact resilience. For example, reduced brain plasticity subsequent to inadequate sleep-dependent brain restoration would certainly impact one's ability to respond and recover from stressor. Consequently, follow-up studies may examine how resilience may be impacted by disruptions to sleep via tasks that measure the experience and recovery from stressors. Existing research from a developmental psychopathology perspective has documented that increased quality sleep appears to be protective against the later development of depressive disorders (Silk et al., 2007). Contrastingly, research in sleep deprivation has also subsequent impairments in tasks that are likely involved in resilience, such as emotion regulation. In light of existing research, it is likely that the relationship between resilience and sleep may be bidirectional.

Future Directions

The studies in this dissertation have provided some evidence that may lead to future research. First, given the heterogeneity in depression, future studies may attempt to replicate findings within particular dimensions of symptoms in depression. If reduced cortical activity during wakefulness is related to negative low arousal states in depression, then cortical activity in individuals who experience catatonic-depression may differ that those who experience more agitated-depression. Similarly, cortical activity may be further pursued as a dimensional factor that may differ between diagnoses involving higher arousal negative affect (e.g., anxiety, mania) than those that involve lower arousal negative states (e.g., depression, dysthymia, chronic fatigue).

Future studies may also examine the influence of sleep interventions in the profile of cortical activity across diagnoses. Cognitive behavioral therapy for insomnia (CBT-I) has the most evidence as a sleep intervention, and has been shown preliminarily to reduce beta activity in insomnia (Cervena et al., 2004). Similar studies can be done examining how CBT-I may influence cortical activity in depression and other mood disorders.

Finally, results from the third study demonstrate that psychological resilience may be one malleable factor that can buffer against the negative affective consequences of sleep disruption. Future studies may validate this by examining experimental tasks that measure emotional and physiological response and recovery from stress in the context of sleep disruption and depression.

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