The Science of Sleep:

An Exploratory Investigation of Sleep Disturbance in the Pathogenesis of Depression

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THE SCIENCE OF SLEEP:
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ABSTRACT

The relationships among stress, sleep, and depression were examined to understand the role of sleep in the etiology of depression. A sample of 335 participants, age range 18-29 years, completed the Pittsburgh Sleep Quality Index (PSQI), the Perceived Stress Scale (PSS), and the Depression Anxiety Stress Scale (DASS-21). Perceived stress, sleep quality, and sleep duration predicted levels of depression. Sleep quality and duration interacted with perceived stress and levels of depression. As sleep quality worsened or duration decreased, levels of depression increased much more rapidly. Sleep disruption should no longer be considered a stress-related outcome, but rather a biological stressor in itself that can lead to the development and maintenance of depression.

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Sleep disorders have been considered for a long time as a cardinal symptom of depression (Adrien, 2002) and while it has long been established that poor sleep quality has adverse effects on mood, motivation, and cognitive functioning (Harvey, 2008), only recently have researchers begun to delineate the relationships among stress, sleep, and mood in both healthy and vulnerable populations. Past research has focused primarily on sleep disruption as a stress-related outcome (Hamilton et al., 2007), but recent findings suggest that sleep disruption may modulate the stress response and should be considered a biological stressor in itself.

Many depressed individuals report that sleep problems are the single most debilitating feature of their disorder (Benca et al., 1997) and more than 65% of individuals diagnosed with depression report at least one complaint related to difficulty falling asleep, frequent awakenings, and/or early morning awakenings (Sbara & Allen, 2009). Sleep disturbance can potentially explain many of the cognitive impairments associated with depression including a negative or threatening interpretive bias towards ambiguous stimuli (Ree & Harvey, 2006) and an overabundance of negatively encoded declarative memories (Walker & van der Helm, 2009). Chronic sleep deprivation has also been shown to enhance dysregulation of the stress response system (Spiegel et al., 1999), which is one of the most robust and reliable findings in depression. Together, this evidence suggests that sleep impairments should be considered a risk factor in the development of depression.

There are converging data to suggest that the American population is not only sleeping less, but that sleep disturbance is becoming exponentially more prominent in all age groups (Steptoe et al., 2008), with nearly a quarter of the U.S. population affected by

sleep disturbance (Opp et al., 2009). Considering that sleep is not the only biological rhythm, it is not surprising that poor sleep quality, associated with chronic sleep debt and/or chronic shifting of the sleep/wake cycle has been shown to have adverse endocrine, immunologic, and metabolic consequences (Harvey, 2008).

Before introducing the current study, a review of literature will be presented to establish sleep, stress, and depression as they have come to be understood through empirical research. The functions of sleep as well as the psychological and biological consequences of sleep impairments will first be discussed, followed by theoretical perspectives of the stress response and biological correlates involved. Next, neuroendocrine correlates of the daily rhythms involved in regulation of the sleep/wake cycle will be presented. Lastly, the conceptual framework surrounding depression will be laid, followed by a comparison of the biological alterations observed in sleep impairments and the etiology of depression.

Sleep: Theoretical Perspectives

Sleep is essential for most organisms, without which life cannot continue for more than a few days, (Bryant et al., 2004) and humans spend approximately one third of a lifetime asleep (Walker & Van der Helm, 2009). Despite the ostensible need we have for its restitution, exhibited by the sometimes impairing homeostatic drive for sleep, it was not until the twentieth century with the development of technology to record electrical activity of the brain, that the underlying neural correlates of sleep were uncovered. This first technology, called the electroencephalogram (EEG) is attributed to the work of Hans Berger who discovered that neural activity in animals could be measured through the electrical changes that reliably reflected such brain activity. By

1938, thirteen years after his initial discovery, Berger had published 23 papers outlining the EEG responses evoked by various stimuli as well as the EEG rhythms that accompany sleep and wakefulness in mammals (Siegel, 2002).

Today, sleep is typically measured using polysomnography (PSG) which combines EEG with electroocculogram (EOG) to measure eye movements, and electromyogram (EMG) to measure muscle tension (Akerstedt, 2006). Through the frequency and amplitude recorded by EEG, sleep can be divided into five stages, with stage five characterized by rapid eye movements (REM), which have been thought to occur during dreaming. Rapid eye movements are absent in stages one through four, which is why sleep is usually categorized into REM or non-REM (NREM) sleep (Siegel, 2002). A typical night's sleep involves four to six cycles of the five stages of sleep, with stages 3 and 4, referred to as slow-wave sleep (SWS), dominating the first half and REM dominating the second half (Walker & Van der Helm, 2009). NREM sleep constitutes approximately 80% of total sleep time and its restorative effects include: energy conservation, CNS restoration, and promotion of immune function.

While researchers have made significant headway in discovering *how* we sleep since the pioneering discovery by Hans Berger, the question *why* we sleep remains "one of the most persistent and perplexing mysteries in biology" (Frank, 2006). All mammals sleep (Siegel, 2005) and so do fish, birds, and even fruit flies. Rats have been shown to die from sleep deprivation before they die from starvation (Siegel, 2005). But *why*? Evolutionary theorists have mapped out some possible adaptive functions of sleep: energy conservation, decreased risk of injury, decreased resource consumption, decreased risk of detection by predators (Siegel, 2005).

Yet for a trait to be adaptive, in general, the benefits should outweigh the costs. While inactivity and energy conservation may be helpful for survival, sleep can also be perceived as largely negative for survival considering that sleeping animals are not only vulnerable to predation, but also that sleep is incompatible with behaviors that ensure survival: eating, procreating, caring for progeny, monitoring the environment for danger, and scouting for prey (Siegel, 2005). Jerome Siegel (2009), a prominent sleep researcher from University of California Los Angeles, has proposed the theory that sleep is a state of adaptive inactivity, whose primary function is to "increase animals' efficiency and minimize their risk by regulating the duration and timing of their behavior." As such, Siegel posits that sleep can be understood as a state of dormancy that is common throughout the plant and animal kingdoms. This statement is qualified with evidence showing that many species have evolved "daily or seasonal dormancy patterns that allow them to anticipate periods that are not optimal for survival and propagation" (Siegel, 2009). According to this hypothesis, if humans are dormant for a third of their lifetime, it is because humans would not benefit from being awake for more than two-thirds.

Evolutionary theorists typically have perceived sleep as a state of inactivity, as sleep has usually been considered throughout history. The appearance of brain imaging techniques has led research toward investigating the functional components of sleep as a restorative process that is vital for survival (Siegel, 2005). Such theorists hold that, because there are so many risks involved for an individual during a dormant, less responsive state, sleep must serve some physiological or neural function that cannot be accomplished during wakefulness (Cirelli & Giuloi, 2008).

Robert Stickgold, a neuroscientist and prominent sleep researcher from Harvard University has proposed the critical function of sleep to be the organization and consolidation of memory (Stickgold et al., 2001). Stickgold's contemporary theory of "offline memory processing" is evidenced by EEG studies displaying neural activity between the hippocampus, the prominent memory center of the brain, and the neocortex, such that experiences accumulated throughout waking life are reprocessed and integrated into other neural structures (Stickgold et al., 2001). A similar hypothesis was first proposed in 1983 when pioneering researchers Crick and Mitchison (1983) proposed the function of dream sleep (REM) to be a reverse learning mechanism such that during REM sleep, undesirable "modes" of interaction in neural networks within the cerebral cortex are eliminated. Crick and Mitchison's theory, thus, suggests that we "sleep to forget." Additionally, sleep has been proposed to play a vital role in affect regulation and may be of considerable importance in the development and maintenance of mood disorders (Walker & Van der Helm, 2009; Harvey, 2008).

The latter proposed function is of primary concern for the current discussion. Perhaps the integral role of sleep in humans that has allowed it to persist throughout our phylogeny involves psychological restoration rather than physiological restoration. In accordance with University of Pennsylvania neuroscientist Marcos Frank's statement (2006), "sleep is for the brain rather than the body," most everyone can attest to the fact that "grumpiness" can result from an inadequate night's sleep. But *why*? What occurs during a somnolent state that leaves us feeling refreshed and rejuvenated? While the entire body undoubtedly benefits from the period of restitution (Cirelli & Giuloi, 2008), interestingly, the most immediate consequence of sleep deprivation is cognitive

impairment (Cirelli & Tononi, 2008). Are the mood alterations associated with poor sleep quality merely secondary to the well-validated cognitive impairments (irritability due to memory inhibition, loss of focus, etc), or is there a restorative function at the neural level that plays a vital role in mood regulation?

While no solitary, vital role for the purpose of sleep will probably ever be revealed, its importance is lucidly illustrated from studies on acute and chronic sleep deprivation as well as from individuals with sleep disorders. Disordered sleep occurs in association with many psychiatric disorders, such as depression, and has been correlated with many medical conditions including cardiovascular, infectious, and inflammatory diseases (Irwin et al., 2002).

Psychological Consequences of Sleep Impairments

Returning to the idea that "sleep is for the brain," several lines of research have shown that sleep is necessary to recover from stress and that the lack of its proper restoration can lead to myriad health consequences, one of which includes the development of depression. It was once commonly believed that individuals who were depressed experienced sleep disturbance as a secondary symptom of depression. Researchers are uncovering evidence to suggest an opposite direction of causation: that sleep disturbance may lead to depression (Perlis et al., 1997). Recovery from acute stress is usually followed by a reparative sleep rebound characterized by an increase in REM sleep and SWS, suggesting the restorative function sleep plays in maintaining homeostasis. Exposure to chronic stress leads to fragmented sleep, probably driven by a stress-induced increase in corticosteroids (Van Reeth et al., 2000).

Johnson and colleagues (2006) explored the direction of association between sleep impairments and major depression in a community-based sample. Structured interviews were conducted to assess sleep impairments and depression in 1,014 participants. Prior depression was not associated with later sleep impairments, however, prior sleep impairments were associated with onset of depression in 69% of comorbid cases after adjusting for gender, race/ethnicity, and any prior anxiety disorder. Similarly, a meta-analysis conducted by Perlis et al. (1997) found that patients who suffer from recurrence of depressive episodes exhibit increased levels of sleep disturbance several weeks prior to the recurrence.

Studies on acute sleep deprivation suggest that the cognitive impairments involved in the lack of sleep may lead individuals to perceive next day stimuli as more threatening (Ree & Harvey, 2006) and emotionally valenced (Walker & Van der Helm, 2009). While ethical restrictions limit humans from participating in prolonged sleep deprivation experiments, studies suggest additive effects over time may lead to health problems, including depression.

Researchers have found salient associations between depression and cognitive impairments as well as alterations in the encoding of declarative memories. Increasingly, research findings are gaining support for a bidirectional relationship between affect regulation and circuits involved in sleep (Harvey, 2008). Individuals have been shown to become increasingly irritable and affectively volatile with increasing sleep deprivation (Harvey, 2008). Research into the role of sleep in regulating psychophysiological reactivity and emotional brain networks, a once commonly overlooked topic in the pathophysiology of depression, is now rapidly emerging.

An investigation by Ree & Harvey (2006) examined the presence of an interpretive bias in sleepy individuals compared with controls. Sleepiness was assessed using the Stanford Sleepiness Scale with sleepy participants scoring 3 or above and not-sleepy participants scoring 2 or below with a final sample of 55 sleepy participants and 23 not-sleepy participants. Participants completed a lexical decision task in which ambiguous sentences were paired with one word that corresponded to each possible meaning of the sentence. For example, a sentence such as "*Rosemary tried to disguise the size of her bags"* was presented and participants were requested to choose whether the word *"shopping"* or "*eyes*" best fit the interpretation of the sentence. The open-ended responses were coded by two judges, according to whether the alternate choice represented a generally threatening interpretation compared to the neutral choice. A significant interaction was found between the sleepiness group and target word type, such that those in the sleepy group responded more quickly (measured in *ms*) to the general threat-consistent target word (*eyes*) than to the general threat-inconsistent target word (*shopping*). The option "*eyes"* may be considered more threatening to a sleepy participant who fears exhibiting noticeable sleep deprivation symptoms such as having bags under the eyes. Individual differences in reaction times are thought to reflect the extent to which a word is congruent with a person's own concerns and cognitions (Ree & Harvey, 2006). The authors have suggested that a sleepiness-linked bias may serve to increase arousal levels in sleepy individuals, which may contribute to the cognitive impairments that are characteristic of sleep disturbance.

There is growing evidence in line with cognitive theories of depression to suggest that depressed individuals have a tendency to interpret ambiguous information in a

negative manner (Beck, 1976), and that such an interpretive bias may play an important role in the development and maintenance of depressed mood. An experiment conducted by Mogg et al. (2005) examined interpretive bias for ambiguous material in clinically depressed individuals using a homophone task. Forty-eight participants (24 depressed without co-morbid anxiety diagnosis and 24 non-depressed) listened to a list of 14 orally presented homophones that had either a negative or a non-negative meaning (e.g. die/dye, weak/week) and were asked to record the word on paper. A significant difference was found in homophone bias scores between the depressed and control groups, such that depressed patients recorded significantly more negative meaning versions of the homophone. It should be noted that a homophone task is susceptible to response bias effects, but the results nonetheless support converging evidence for an interpretive bias of ambiguous stimuli in depressed individuals.

Memory impairments have been observed in depression (Burt et al., 1995) and the relationship between sleep and memory consolidation is well documented (Walker & van der Helm, 2009). A recent investigation by Walker & Tharani (2009) tested the effects of acute sleep deprivation prior to a learning session of emotionally valenced words. Participants who were sleep deprived demonstrated a 40% deficit in memory encoding relative to participants who had slept normally prior to learning. In participants who had slept (control group), both positive and negative stumuli were associated with superior retention levels relative to the neutral condition, consistent with the notion that emotion facilitates memory encoding (Phelps, 2004). In the sleep-deprived group, a severe encoding impairment was evident for neutral and especially positive emotional

memories, with sleep-deprived participants exhibiting a significant, 59% retention deficit relative to participants in the control condition (Walker & Tharani, 2009).

Most interesting was the relative resistance of negative emotional memory to sleep deprivation, for which markedly smaller and nonsignificant impairment was evident. Thus, the encoding of negative memory appears to be more resistant to the effects of prior sleep loss offering novel memory insights into affective mood disorders that express co-occurring sleep abnormalities (Buysse, 2004). The findings by Walker & Tharani (2009) can be seen to support Crick & Mitchison's "sleep to forget" theory such that without sleeping, relatively more, non-salient information was available. However, if one considers that sleep loss represents a vulnerable state, having greater access to negative memories could function to keep a sleep-deprived organism away from potential danger.

Although based on findings from acute sleep deprivation, it is noteworthy that chronic accumulated sleep debt associated with depression may impair the ability to form and retain memories of positive (and neutral) affective valence, yet leave preserved the formation and hence long-term dominance of negative experiences (Walker & van der Helm, 2009). Such an encoding bias would result in a perceived autobiographical history dominated by negative life events, despite being potentially filled with both positive and negative daily experiences. Indeed, this imbalance may provide a converse explanation for the higher incidence of depression in populations expressing impairments in sleep. The experiment conducted by Walker and Tharani (2009) thus gives evidence that sleep deprivation is associated with an enhanced bias toward negative encoding of memories that may contribute to the development of depression.

In addition to the damaging effects sleep disruption may have on learning, cognitive, and memory processes, researchers have observed alterations in neuroendocrine systems that may result from acute and chronic sleep disturbance, with salient implications for stress-related mood disorders, namely depression. The stress response and circuits involved in sleep regulation, both adaptive biological systems, function to react and restore an organism within its environment (Van Reeth et al., 2000). In the past there has been a paucity of research to delineate the interactions between the stress response system and sleep regulation. With the spawn of inter-disciplinary research fields that strive to integrate the neural, endocrine, and immune functions of an organism such as psychoneuroimmunology, researchers are uncovering the pathways of communication between the stress response system and sleep regulation that may have therapeutic implications. Additionally, a greater understanding of the feedback between stress and sleep systems could shed light on the high comorbidity between sleep disturbances and mood disorders, both posited to be preceded and maintained by stress (Harvey, 2008).

Stress: Theoretical Perspectives & Biological Correlates

In 1935, Hans Selye published "A Syndrome Produced by Diverse and Nocuous Agents" which outlined the concept of "stress" as the "nonspecific result of any demand upon the body" that can be produced from a variety of dissimilar situations- emotional arousal, effort, fatigue, pain, fear, concentration, humiliation, loss of blood, and even great and unexpected success, (Selye, 1936). Selye further developed the concept of stress by outlining the "general adaptation syndrome," the stages of physiological response to stress that is still commonly referred to today.

The general adaptation syndrome (GAS) can be organized into three stages beginning with (1) the alarm reaction, during which numerous biological systems including the neuroendocrine axis are engaged. The state of alarm cannot be maintained very long, and if the organism survives it will transition into (2) the stage of resistance. The stage of resistance is characterized by the activated biological systems returning to normal. If the noxious stimulus persists, the acquired adaptation is lost and the organism enters into (3) the stage of exhaustion that can lead to illness or death of the organism (Selye, 1936).

Selye's "alarm" stage of the stress response is known to elicit activation of the sympathetic nervous system (SNS). The SNS initiates a "flight or fight" response within seconds of a threat, allowing an organism to be aroused and to generate energy in order to escape ("flight") or confront ("fight") the stressor. Activation of the SNS results in a great energy expenditure including mobilization of energy (free fatty acids, glycerol, glucose, amino acids) from storage units (triglycerides, glycogen, proteins) and stopping all further energy storage until the stressor subsides. Activation of the SNS is concurrently characterized by release of catecholamines such as epinephrine, increase in cardiovascular activity, as well as suppression of digestion, growth, reproduction, inflammatory responses, and immunity (Van Reeth, 2000).

The "resistance" stage of Selye's GAS concerns the "rest and digest" phase elicited by the parasympathetic nervous system (PNS). Functionally complementary to the SNS, the PNS acts to reinstate homeostasis in the organism by release of acetylcholine to resume normal cardiac activity, increase intestinal and gland activity, and decrease blood pressure to normal functioning (Vedhara & Irwin, 2005).

If the noxious stimulus persists, the organism enters into the third and final stage of the GAS, the stage of "exhaustion." The onset of exhaustion has been proposed to occur upon depletion of adaptation energy stores, characterized by enhanced activity of the hypothalamic-pituitary-adrenal axis and pathophysiological changes in the immune system and gastrointestinal tract. Such changes increase the organism's susceptibility to infectious agents and gastrointestinal ulcers resulting ultimately in illness or death of the organism (Selye, 1936).

Though the stress response system has evolved in such a way to be capable of recognizing and responding to potential threats and enabling an organism to return to homeostasis, dysregulation is known to occur when stressors are prolonged beyond what is adaptive for an organism and feedback mechanisms fail in restoring equilibrium which can lead to myriad health consequences (Vedhara & Irwin, 2005). Sleep can be seen as a paramount restoring mechanism of an organism. Some of the restorative functions of sleep include the elimination of oxidative stress that is accumulated throughout a waking period as well as an increased secretion of hormones such as growth hormone and an increase of immune secretions.

While Selye's GAS theory contributed greatly to the understanding of "stress," more recent research has begun to illuminate the variability present in the stress response cascade such that activation of the stress HPA axis does not follow a generalizable, uniform model. Kemeny (2003) has outlined the integrated specificity model to suggest that the biological response of an organism is highly dependent upon the organism's cognitive appraisal. Factors such as perceived control, social status, and perceptions of threat versus challenge have shown to significantly impact an organism's

psychobiological response to stress For example, humans who are exposed to stressors in a laboratory setting demonstrate increased HPA activation if the stressors are uncontrollable than if they are controllable. Similarly, it has been demonstrated that demanding performance tasks elicit greater HPA activation when one's social status or social self-esteem is threatened by performance failures (Kemeny, 2003).

Additionally, McEwen (2006) uses the term "allostasis" to describe the activation of neural, neuroendocrine and neuroendocrine-immune mechanisms in the face of potentially stressful challenges that allows an organism to adapt. This "stability through change," as allostasis has been described, is an essential component of maintaining homeostasis. Accordingly, McEwen (2006) has proposed that individual differences in response to challenge depend not only on the 1) appraisal of the situation, but also on 2) the condition of the body and its ability to withstand repeated adjustive demands. When allostatic systems are overworked or fail to shut off after the stressful event is over, "allostatic load" is seen to occur. Allostatic load can be altered via health-damaging and health-promoting behaviors such as smoking, drinking, choice of diet, exercise and most importantly for the current discussion, adequate sleep.

Sleep, which functions to restore an organism within its environment, appears to be an important determinant in the health and resilience, as a biobehavioral resource that minimizes allostatic load (Hamilton et al., 2007). With a robust and well-documented association between stress and the development of depression (Rooij et al., 2009), behavioral contributions that may function to decrease allostatic load should be considered of paramount importance for homeostasis of an organism, *especially during periods of repeated adjustive demands.* While Selye's GAS may not be as "general" as

once believed, there is evidence to suggest that endogenous stressors including sleep deprivation and infection are considered similarly by biological resources, as are exogenous stressors originating from "outside" an organism (McEwen, 2006). Sleep, therefore, may be considered to play a moderating role in the stress/depression relationship. Conversely, the most salient evidence for this relationship is seen when sleep disturbance occurs, leaving an organism vulnerable to a stress related disorder such as depression.

Among the responses elicited by stress are activation of the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenal-medullary (SAM) axes. The hallmark sympathetic "flight or fight" response is characterized by global activation of the SAM axis and features typical physiological and behavioral activation including increased heart rate, increased blood pressure, and rapid breathing, along with release of catecholamines including epinephrine from the adrenal medulla. The SAM axis is characterized by its speed of onset which occurs within seconds of a stessful stimulus, its ability to begin in anticipation of an event being stressful, and its interaction with the HPA axis (Van Reeth, 2000).

Within minutes of response to stressful stimuli, the hypothalamic-derived releasing hormones corticotrophin-releasing hormone (CRH), growth-hormone-releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH) stimulate the synthesis and release of anterior pituitary adrenocorticotrophic hormone (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), leutinizing hormone (LH), and follicle- stimulating hormone (FSH), respectively. These hormones are then released into the circulatory system where they act on specific tissues.

ACTH specifically stimulates the production of cortisol from the cortex of the adrenal gland. Cortisol has been identified as the "main effector hormone of the HPA axis, gaining access to every cell in the body and influencing many essential stress-related cellular processes" (Vedhara & Irwin, 2005). The cortisol response is much slower than activation of the SAM axis, with peak levels not seen for 15-20 minutes after the onset of the stress. Early actions of the HPA system provide additional energy resources for the stress response, while slower gene-related effects over the next few minutes to hours serve to restrain ongoing actions of the stress response which, if left unchecked, may prove to be unsustainable for the organism. Additionally, corticotrophin-releasing hormone (CRH) has been shown to activate release of norepinehprine, inducing increased levels of arousal, which may have salient implications for stress-related sleep disturbances.

Increased levels of cortisol provide negative feedback to inhibit further release of CRH and ACTH. The hippocampus, which is endowed with high levels of receptors for adrenal steroids,

is also a regulator of the stress response (McEwen, 2006) and exerts a large inhibitory effect to promote shut-off of the HPA axis. Acute stress that elevates adrenal steroids has been shown to suppress neuronal mechanisms that subserve short-term memory involving the hippocampus, though the effects are reversible and relatively short-lived. Prolonged stress coupled with chronic increased levels of glucocorticoids, however, can cause atrophy of hippocampal dendrites and subsequent death of neurons (McEwen, 2006). The effects of glucocorticoid excess on the hippocampus are two-fold. Considering that the hippocampus is the primary brain region involved in the consolidation of memories and

is also involved in the appraisal of stressors, hippocampal damage can result in both memory impairments along with impairments in responding to stressors (McEwen, 2006).

Neuroendocrine Regulation of the Sleep/Wake Cycle

Several hormones of the HPA axis show a daily rhythm. For example, the daily rhythm of cortisol secretion is referred to as the ultradian rhythm, a biological rhythm that is repeated throughout a 24-hour circadian day. Other ultradian rhythms include heart rate, thermoregulation, urination, bowel activity, and appetite, but the cortisol ultradian rhythm, specifically, is marked by a morning zenith and an evening nadir (Bryant et al., 2004). Cortisol can be seen as a "wakefulness" or "arousal" hormone that prepares us for the day, receding during the night when sleep occurs. The nadir for cortisol occurs around midnight (Buckley & Schatzbeg, 2005) and cortisol levels begin to rise about 2-3 hours after sleep onset and continue to rise into the early waking hours.

Slow wave sleep (SWS), which dominates the first part of the night, is characterized by a pulsatile release of growth hormone. Growth hormone has been proposed as a putative inhibitor of the HPA axis, as CRH release is seen to be inhibited during SWS when circulating stress hormones reach diurnal a minimum. Elevated CRH levels have been shown to increase sleep EEG frequency, possibly by activation of epinephrine, thereby decreasing SWS and increasing light sleep and wakefulness (Buckley & Schatzberg, 2005). Nocturnal awakenings are associated with pulsatile releases of cortisol (Buckley & Schatzberg, 2005). The peak of cortisol has been shown to occur around 9:00 AM and is marked by a rapid rise in cortisol and ACTH that continues for approximately 60 minutes.

The ultradian rhythm of cortisol is susceptible to alterations if hyperarousal of the HPA axis occurs, most likely from stress or sleep deprivation. In a study by Rosmond and colleagues (2002), it was shown that the HPA-axis in healthy individuals is characterized by a wide ultradian rhythm, a discrete but small response to an acute stress, and an appropriate suppression of cortisol levels following stress. Chronically stressed individuals displayed a decreased ultradian variability and inadequate cortisol suppression after acute stress, indicating an altered pattern of secretion and impaired negative feedback with resultant cortisol hypersecretion. The effects of hypercortisolism in the brain can lead to cognitive dysfunction (Bhagwagar, 2003), depression, anxiety, along with a cascade of the metabolic syndrome characterized by bone loss, obesity, hypertension, and insulin resistance (Vedhara & Irwin, 2005).

The term "circadian" means "about one day" (Harvey, 2008) and refers to the biological rhythm that has evolved in response to the 24-hour cycle of the sun. Sunlight is the primary zeitgeber, or "timegiver" of the circadian rhythm that enables mammals to be synchronized with the outside world. The biological "time clock" that entrains an organism to its environment is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus (Harvey, 2008). Cells in the SCN stimulate the pineal gland to modulate body temperature and production of melatonin, the primary sleep inducing hormone (Harvey, 2008). Melatonin follows a 24-hour rhythm with the highest point at night and lowest in the morning, functionally and temporally opposite to the rhythm of cortisol secretion. This active process of entrainment allows mammals the flexibility to change environments, such as different time zones, and to adapt to new light/dark phases.

Sleep is under the dual control of circadian rhythmicity as well as a homeostatic process relating to the depth of sleep and the duration of prior wakefulness. The homeostatic process is proposed to involve a putative sleep factor that increases during waking and decays exponentially during sleep (Van Cauter et al., 2000). While the circadian timing of sleep is less often shifted, with the exception of time zone changes during travel, and the bi-yearly daylight savings, the homeostatic drive for sleep is more easily amenable to being shifted (Wirz-Justice, 2006).

Most everyone can attest to becoming more aware of their homeostatic drive for sleep after having slept for an extended period during the day with subsequent wakefulness during the quiescent period. Chronic shifting of the homeostatic drive for sleep can lead to adverse metabolic, endocrine, and immune functioning (Wirz-Justice, 2006) as the onset of sleep is seen to initiate the release of growth hormone as well as inhibit the HPA axis (Van Cauter et al., 2000). In both animals and humans, the HPA axis plays an important role in sleep-wake regulation and in alterations of the sleep-wake cycle after acute or chronic stress including sleep deprivation. There is a clear and robust temporal association between sleep-wake states and activity of the HPA axis (Van Reeth, 2000) such that increases in melatonin secretion promote feelings of sleepiness and increases in secretion of cortisol promote wakefulness.

Depression: Epidemiology, Etiology, & Associations with Sleep Impairments

Depression can be described as a condition that primarily involves a disturbance of mood, and this affective disturbance is characterized by a mood that is sad, hopeless, discouraged, or simply depressed (American Psychiatric Association, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 2000),

major depressive disorder (MDD) is characterized by one or more episodes with five or more of the following symptoms most of the day, nearly every day for at least two weeks: 1) depressed mood; 2) markedly diminished interest or pleasure in most activities; 3) significant weight loss or weight gain; 4) insomnia or hypersomnia; 5) psychomotor agitation or retardation; 6) fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate; and 7) recurrent thoughts of death (APA, 2000).

With regard to epidemiology, the lifetime prevalence of the depression is 6% to 10% and begins most commonly in the 20's and 30's. Risk factors for depression include prior episodes of the illness, family history of depression, prior suicide attempts, lack of social support, medical comorbidity, stressful life events and current substance abuse. Additionally, women are at twice the lifetime risk as men, and the postpartum period increases the risk of first onset of the illness and a recurrence in those already ill (Shaffrey et al., 2003).

Research has suggested that sleep problems should be classified as a biological stressor and not just a consequence of stressful events. When rats have been induced to sleep deprivation there was an observable activation of the HPA axis (Bryant et al., 2004). Shift work and disruption of the normal circadian clock have been linked with breast cancer and cardiovascular abnormalities as well as the development and maintenance of mood disorders (Harvey, 2008). Sleep deprivation represents a stressful experience that, via activation of the major stress hormonal systems, is likely to alter health function.

The absence of sleep onset has been shown to associate with higher cortisol levels at the quiescent period. Given that the day-long decrease of cortisol levels partially

reflects the recovery of the HPA axis from the early morning circadian stimulation that occurs in response to increased CRH drive during the second part of the night, elevation of evening cortisol levels might thus reflect an alteration of the rate of recovery of the HPA axis from the endogenous challenge that is likely to involve impairment of the feedback regulation of the HPA axis (Van Reeth et al., 2002).

Spiegel et al. (1999) assessed activity of the HPA axis in 11 young men after time in bed had been restricted to 4 hours per night for 6 nights. Sleep-debt measures were compared with the sleep-recovery period when participants were allowed 12 hours in bed per night for 6 nights. Both salivary cortisol and total plasma concentration of cortisol were measured. Along with decreased glucose tolerance and increased activity of the SNS, the sleep debt condition was characterized by increased levels of cortisol concentrations in the afternoon and evening. The rate of decrease of free cortisol concentrations between 4 PM and 9 PM was approximately six times slower in the sleep-debt condition than in the sleep recovery condition (Spiegel et al., 1999).

That sleep disruption mirrors hypercortisolism associated with chronic stress suggests that the ability of the HPA axis to recover from exogenous stimulation would be affected by sleep loss. Due to the deteriorating effects of hypercortisolism on the hippocampus, and that the hippocampus is the primary feedback regulator of cortisol, sleep deprivation coupled with stress may promote further alterations in the feedback mechanisms of the HPA axis. Chronic sleep loss may therefore accelerate the development of metabolic and cognitive consequences of glucocorticoid excess, such as cognitive deficits and decreased carbohydrate tolerance (Van Reeth, 2000).

Interestingly, in addition to being a paramount structure in feedback regulation of cortisol, the hippocampus is responsible for memory organization and consolidation. As sleep is known to play a considerable role in the consolidation of declarative memories (Born et al., 2000), sleep deprivation could affect the hippocampus two-fold, modulating both cognitive resources and receptor function. Hippocampal volume reduction has also been observed in major depression. Bremner (2000) demonstrated that participants with depression had a statistically significant 19% smaller left hippocampal volume than control subjects, implying the learning and memory impairments that may be involved in depression.

Similarly, depression is marked by alterations in the HPA axis that are similar to chronic exposure to stress. Overactivity of the HPA axis within individuals with major depressive disorder has been documented since the late 1950s (McKay et al., 2010). Cortisol hypersecretion is regarded as important in the pathophysiology of major depression and the underlying dysregulations of the HPA axis in depression and chronic stress seem to follow a similar pattern. Both conditions are characterized by increases in cortisol secretion which is proposed to reflect altered capacity or function of glucocortocoid receptors (Pruessner et al., 2003). More refined analyses of the HPA system have revealed that impairments in glucocorticoid receptors result among other changes, in increased production and secretion of CRH (Holsboer, 2000). Findings such as these have led to the hypothesis that impaired glucocorticoid receptor signalling is a key mechanism in the pathogenesis of depression (Holsboer, 2000).

Increased sleep latency, decreased sleep continuity (increased time awake between sleep onset and final awakening), early morning awakenings, and nonrestorative

or poor quality sleep represent the most commonly encountered subjective sleep complaints in depressed individuals (Winokur et al., 2001). Polysomnographic studies have found reliable objective alterations in sleep architecture in depressed patients (Winokur et al., 2001). In addition to corroborating the subjective sleep complaints including increased latency, increased awakenings, and early morning awakenings, PSG measures have observed decreased SWS, reduced REM latency, increased REM during the first half of the night (when SWS usually dominates) and overall increased REM density.

Both objective and subjective sleep measures can be seen to reflect alterations in the HPA axis in depressed patients. Effects of stress hormones on sleep architecture have been demonstrated through exogenous administration of each of the major mediators of the HPA axis. Pulsatile administration of CRH has been shown to produce reduced SWS and reduced REM latency along with increases in the amount of shallow sleep (stages I and II) (Holsboer, 1999;Van Reeth, 2000). In line with the hypothesis that increased CRH levels are present in depressed patients and this may play a causal role in observed sleep disruption, clinical studies investigating a CRH-receptor-antagonist in patients with depression have shown an improvement in sleep quality and increased SWS shortly after initiation of treatment (Schmind et al., 2008).

A meta-analysis conducted by Burke et al. (2005) showed that depressed patients, compared to non-depressed controls, exhibited a blunted cortisol response to acute stress and impaired stress recovery. During the “recovery” period, depressed patients’ cortisol levels remained higher when compared to controls. This evidence further implicates impaired feedback of the HPA axis in depression (Burke et al., 2005).

The rise in salivary-free cortisol that follows waking is a simple and reliable means of assessing the dynamic activity of the HPA axis activity and may therefore offer advantages of the HPA axis activity over isolated measures of basal salivary cortisol. Pruessner et al. (2003) examined the relationship between depressive symptomatology, measures of stress, and the cortisol response to awakening in healthy male college students. A positive association between elevated cortisol levels after awakening and the self-reported severity of depressive symptoms was demonstrated.

Similarly, Bhagwagar and colleagues (2005) investigated the pattern of waking salivary cortisol in 20 unmedicated acutely depressed subjects and 40 healthy controls. It was found that patients with acute depression secreted approximately 25% more cortisol than controls. It was concluded that depressed patients have increased early morning cortisol secretion. If depressed patients have higher levels of cortisol, potentially throughout the night and in the early morning, this may explain the sleep disturbance that is commonly seen in conjunction with depression.

Bhagwagar (2003) found similarly increased cortisol levels after waking in medication-free euthymic, or not depressed, subjects with a past history of recurrent depression. This suggests that hypersecretion of salivary cortisol in relation to waking may represent a trait marker of depression because it appeared to persist when patients were clinically recovered. Authors present data supporting the hypothesis that HPA axis hyperactivity is not a simple consequence or epiphenomenon of depression, but on the contrary that it is a risk factor to the development of depression.

Consistent with the notion that impaired glucocorticoid receptor function is crucial for HPA axis hyperactivity in depression, anti-depressant treatment has been

shown to increase glucocorticoid receptor expression, glucocorticoid receptor function and glucocorticoid receptor-mediated HPA axis feedback inhibition in laboratory animals as well as in humans, thereby reducing resting and stimulated HPA axis activity (Pariante, 2008). Finally, normalization of glucocorticoid receptor function by antidepressant treatment has been found to be a significant predictor of long-term clinical outcome (Pariante, 2008).

Research findings are burgeoning that corroborate a bidirectional relationship between sleep impairments and daytime symptoms of depression. Harvey (2008) has proposed an escalating "vicious" cycle, such that disturbance in mood during the day interferes with nighttime sleep and conversely, the effects of sleep disturbance contribute to mood-regulation difficulty along with cognitive and memory impairments. In this light, sleep can be seen as the common denominator: increases in sleep quality improve daytime functioning and mitigate depressive symptoms, whereas sleep impairments decrease daytime functioning and exacerbate symptoms of depression.

Considering the comparable cognitive, memory, and biological impairments associated with sleep disturbance and depression, the current exploratory study attempted to bolster previous findings by investigating the relationships among stress, sleep, and depression. It was expected that stress, sleep quality, and sleep duration would predict levels of depression, with increases in stress and decreases in sleep quality and duration predicting increased symptoms of depression. Additionally, sleep quality and duration were analyzed for their contributing role in the stress/depression relationship. If increases in sleep predict lower levels of depression, and decreases in sleep predict higher levels of

depression, then the current study will provide further evidence for the role of sleep in the development and maintenance of depression.

Method

Participants

A total of 426 participants from a small liberal arts college in southwest Florida responded to a survey. Ninety-one participants were omitted on the basis of incomplete answers. The final sample consisted of 335 participants, of which 213 were female and 122 were male. Participants were recruited by convenience and did not receive incentive for participation.

Materials

PSQI - The Pittsburgh Sleep Quality Index is a well-validated, widely used 19-item self-report measure developed in 1989 to examine sleep quality over the previous month. It contains seven sub-scales measuring domains such as subjective sleep quality, sleep latency, sleep duration, and sleep disturbance, which combine to yield a global score of sleep quality. Global sleep quality scores are continuous (range 0-21) with higher scores reflecting poorer sleep quality, and scores less than 5 indicating good sleep (see Appendix A). The PSQI has been demonstrated to have high internal consistency (Cronbach's alpha = 0.83), test-retest reliability (0.85-0.87) (Backhaus et al., 2002) as well as a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p < 0.001$) in distinguishing good and poor sleepers. (Buysse et al., 1989)

PSS - The Perceived Stress Scale is a 10-item self-report questionnaire designed to measure perceptions of stress over the past month. Responses are given on a 5-point Likert scale (see Appendix B) with half of responses reverse scored to yield a single

score. Scores range from 0-40 with higher scores reflecting higher levels of perceived stress. Because levels of appraised stress are influenced by alterations in daily hassles, major stressful events, and coping resources, the predictive validity of the scale is expected to decrease after a period of four to eight weeks. Because the PSS was not designed as a diagnostic tool, no clinical cut-off points are available. A large sample (N = 2,387) collected by Cohen & Williamson (1988) found that the mean score for participants between the age of 18 and 29 was 14.2 (SD = 6.2).

Higher PSS scores are associated with failure to quit smoking, failure among diabetics to control blood sugar levels, and greater vulnerability to stressful-life-event-elicited depressive symptoms (Cohen, 1994). Additionally, an investigation by Cohen et al. (1983) showed that scores on the PSS were moderately correlated with number of stressful life events in a college sample and a community sample. In the same sample, Cronbach's alpha for the PSS was .85 in the college sample and .86 in the community sample.

An investigation by Cohen et al. (1993) assessed perceived stress levels in 394 healthy participants before participants were exposed to a common cold virus. Participants were quarantined for two days prior to and 7 days following the viral challenge in a large apartment

and monitored for the development of biologically verified clinical illness. Consistent with the notion that psychological stress increases an individual's susceptibility to infection, higher scores on the PSS were associated with greater risk of developing a cold. In short, the PSS has been shown to reliably measure perceptions of stress over the past two weeks.

DASS-21 - The Depression Anxiety Stress Scale is a shortened version of Lovibond & Lovibond's (1995) original 42-item questionnaire of depression, anxiety, and stress (DASS). Composed of 21 Likert-scale questions with seven questions for each subscale, the DASS-21 examines the affective components of stress, anxiety, and depression over the past week. Higher scores signify increased severity of symptoms with scores ranging between 0-14 (see Appendix C).

An investigation by Henry & Crawford (2005) tested the psychometric properties of the DASS-21 subscales with 1,794 non-clinical participants. Using Cronbach's alpha, the Depression subscale was shown to have an internal reliability of .88.

Henry & Crawford (2003) also investigated the convergent validity of the DASS-21 by calculating Pearson product moment correlations between each of the DASS-21 subscales with two independent measures of anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), and the Personal Disturbance Scale (sAD) (Bedford & Foulds, 1978). With a non-clinical sample of 1,771 participants, the depression subscale correlated with the sAD depression scale (.78). The correlation between the depression subscale of the DASS-21 and the HADS depression scale was .66. The correlations between the DASS-21 and the sAD and HADS both exceeded the correlation found between the sAD depression scale and the HADS depression scale ($p <$ .001) suggesting that the convergent validity of the DASS-21 is superior to other scales examined.

Procedure

Participants were provided a link via E-mail to access an online survey using SurveyMonkey, which they were told was designed to assess their sleep habits and stress

over specified periods of time. The survey included the PSQI, followed by the PSS and DASS-21. After providing informed consent, participants were requested to read each statement and to indicate the best answer by clicking on the response. Upon completion, participants were debriefed and thanked for their participation.

Statistical Analyses

Pearson *r* correlations were performed to examine the correlation coefficients between each of the predictor variables and depression. A multiple regression correlation was conducted on two models (1) *Depression = Perceived Stress + Sleep Quality* (2) *Depression = Perceived Stress + Duration* to ascertain the predictive validity of the each. Semi-partial correlations were also performed on each model to determine the unique contribution of each predictor variable on depression.

Significant interactions were analyzed using *ITALASSI*, a downloadable statistical analysis program that allows the graph to be rotated and viewed from all angles to further elucidate the relationships between the three variables. A visible plane distortion is indicative of an interaction (see Figure 1 and Figure 2).

Results

The mean score obtained for the Pittsburgh Sleep Quality Index (PSQI) was 8.29 (*SD* = 3.02, *range* = 2-21) which is markedly high when considering a PSQI score greater than 5 is thought to indicate clinical sleep impairments (Buysse et al.,1989). The sample mean score was significantly higher than the clinical cutoff for low quality sleep, $t(337) = 20.06$, $p < .0001$. The mean score obtained for the Perceived Stress Scale (PSS) was 19.0 (*SD* = 6.76, *range* = 3-38) which is significantly greater than the population average of 14.2, $t(376) = 13.68$, $p < .0001$, for individuals between the age of 18 and 29, (Cohen &

Williamson, 1988). Higher scores indicating higher levels of Perceived Stress in the sample population may be somewhat reflective of the rigorous academic experience at New College of Florida during finals when data were collected. While some authors have chosen to group subjects into categories based on scores on the PSS and PSQI (e.g. Low Perceived Stress/High Perceived Stress; Poor Sleep Quality/Good Sleep Quality), this procedure reduces information. For this reason, all variables were kept continuous. The mean score for the Depression subscale of the DASS (DASS_D) was 5.8 (SD = 4.22), with females (M = 5.85, SD = 4.19) scoring similarly to males (M = 5.77, SD = 4.28) in the mild depression range (5-6.5) reported by Lovibond & Lovibond (1995).

Table 1 shows all Pearson r correlations among the PSQI, PSS, and the DASS_D. Poor Sleep Quality was associated with higher levels of Perceived Stress $r(334) = .506$, $p < .0001$ and higher levels of Depression $r(328) = .500$, $p < .0001$. Additionally, increases in Perceived Stress were associated with higher levels of Depression $r(367) = .658$, $p < .0001$, supporting the well-documented relationship between stress and depression (Shaffrey et al., 2003).

Poor Sleep Continuity was associated with higher levels of Depression $r(365) = .229$, $p < .0001$. Sleep Continuity refers to time awake between sleep onset and final awakening. The lower the score on the Sleep Continuity measure, the fewer awakenings after sleep onset, accounting for the positive (rather than negative) correlation between Sleep Continuity and Depression.

Decreases in Duration were associated with higher levels of Perceived Stress $r(358) = -0.302$, $p < .0001$. Additionally, decreases in Duration were associated with

higher levels of Depression, though the strength of the relationship was weak $r(348) = -0.184$, $p = .0006$.

Relationship of Depression with Perceived Stress and Sleep Quality

Perceived Stress and Sleep Quality had moderately strong predictive validity for Depression ($R^2 = .487$, $p < .0001$). Semi-partial correlations were used to evaluate the unique contribution that Perceived Stress and Sleep Quality had on Depression. Perceived Stress had a strong unique contribution ($b = .166$, $p < .017$, $sr^2 = .435$, $p < .0001$) followed by Sleep Quality ($b = -0.146$, $p = .419$, $sr^2 = 0.039$, $p < .0001$). Lower Sleep Quality scores indicate *better* sleep quality, accounting for the negative contribution that Sleep Quality has on depression.

There was a significant interaction between Perceived Stress and Sleep Quality ($b = 0.021$, $p = .0055$) (see Figure 1). Increases in Perceived Stress and decreases in Sleep Quality (higher scores) predicted higher levels of Depression, but Depression levels increased much more rapidly as Sleep Quality decreased (scores became greater).

Relationship of Depression with Perceived Stress and Sleep Duration

Perceived Stress and Sleep Duration had moderately strong predictive validity for Depression ($R^2 = .424$, $p < .0001$). Semi-partial correlations were used to evaluate the unique contribution that Perceived Stress and Sleep Duration had on Depression. Perceived Stress had a strong unique contribution ($b = 0.738$, $p < .0001$,$sr^2 = .416$, $p < .0001$). Sleep Duration did not yield a significant contribution.

There was a significant interaction between Perceived Stress and Duration ($b = .048$ $p = .035$). Increases in Perceived Stress and decreases in Duration predicted higher

levels of Depression, but Depression levels increased more rapidly as Duration decreased (Figure 2).

Discussion

The goal of the present study was to examine the relationships among perceived stress, sleep quality and duration, and depression in a sample of college students. The results supported the hypotheses that perceived stress, sleep quality, and sleep duration would predict levels of depression. Additionally, the results supported the hypothesized moderating role that sleep would play in the stress/depression relationship. Participants who reported worse sleep quality or shorter sleep duration were found to exhibit more symptoms of depression than participants with equal amounts of stress who reported better sleep quality and higher average sleep duration.

While all data were correlational, obscuring the direction of causation, previous research has found sleep impairments to precede the development of depression (Johnson et al., 2004). In line with evidence that sleep impairments represent a biological stressor evidenced by increased activation of the HPA axis (Van Reeth et al., 2002) that may be involved in the pathophysiology of depression, the current study found decrements in sleep quality correlated with increased symptoms of depression.

Additionally, sleep continuity, a measure of time awake between initial sleep onset and final awakening correlated with symptoms of depression. Decreases in sleep continuity were associated with increases in depression. Nocturnal awakenings have been observed to cause a pulsatile release of the cortisol (Buckley & Schatzberg, 2005). An increase in sleep fragmentation may thereby increase nocturnal levels of cortisol, the wakefulness promoting hormone, when cortisol is supposed to be at a diurnal minimum.

Decreases in sleep continuity have been observed in depressed individuals with elevated levels of CRH. Levels of CRH are at their lowest during slow wave sleep (SWS), and elevated levels have been shown to be associated with decreased SWS and increased light sleep (stages 1 and 2), possibly by activation of epinephrine. Considering that light sleep, compared to SWS, is characterized by a decreased arousal threshold, elevated levels of nocturnal CRH could be a mechanism through which depressed individuals experience increased sleep fragmentation (Buckley & Schatzberg, 2005).

The present findings corroborate the role of perceived stress in the development and maintenance of depression. While stressful life events have been shown to precede the onset and relapse of depression (Shaffrey et al., 2003), objective measures of stress are limited in that they cannot account for variability among individuals in appraising and reacting to stressful experiences (Cohen, 1994). For example, an employment promotion may be considered a positive life event on an objective measure of stress, but perhaps the employee had to move to a new city to work in a position that was far less predictable or rewarding. In this case, while an objective stress measure would deem the promotion to be a positive event, a subjective measure would more accurately tap into how the event was appraised by the individual. Stress theorists have emphasized the role of appraisal in responding to events since the concept of stress was first outlined by Hans Seyle (1936). An individual who perceives an event as threatening, uncontrollable, and unpredictable is likely to elicit a greater physiological stress response than someone who perceives the event as challenging, controllable, and predictable, though the events are similar (Kemeny, 2003, Cohen, 1994).

While Perceived Stress was seen to have a greater unique contribution to Depression than either Sleep Quality or Duration, evidenced by larger semi-partial correlations, both models yielded significant interactions between Perceived Stress and Sleep, supporting the moderating role of sleep in the stress/depression relationship. Because perceptions of stress may increase following sleep impairments, future research in this area should measure objective and subjective stress to determine how sleep may mediate the two. Sleep has been proposed to function as a biobehavioral resource that minimizes allostatic load (Hamilton, 2007). If this is true, then restorative sleep should allow an individual to experience objective stress with less increase in perceived stress. On the other hand, as sleep impairments are seen to increase allostatic load (McEwen, 2006), an individual with impaired sleep would be more likely to report greater perceived stress to a similar objective stressor.

In accordance with McEwen's theory of stress, individual differences in response to challenge depend not only on appraisal of the stressor, but also on the condition of the body and its ability to withstand repeated adjustive demands. Sleep impairments activate the stress response system, increasing allostatic load and decreasing resiliency, limiting the ability of an individual to experience increases in stress before illness occurs (McEwen, 2006).

Stress-related disorders including depression can be compared with Selye's final stage of the GAS, the stage of "exhaustion." The biological systems that maintain homeostasis, notably the HPA axis, are no longer functioning to allow an organism to adapt within its environment.

Rather, allostatic systems have become overworked and fail to shut off properly (McEwen, 2006), evidenced by impaired glucocorticoid feedback with concomitant hyperarousal of the HPA axis.

The current study has important implications for the role of sleep in the development and maintenance of depression. Sleep impairments should be considered a "red-flag" for the development of depression. Individuals with a past history or family history of depression should be especially conscientious to get restorative sleep, since sleep disruptions represent a salient risk factor for dysregulation of the HPA axis, a hallmark biological marker observed in depression. Additionally, treatment of sleep disturbance could prevent the development of depression, and reduce the likelihood for relapse among vulnerable populations. Lastly, because comorbid conditions are more difficult to treat and indicate a poorer prognosis than a primary disorder alone (Johnson et al., 2007), health practicioners should pay particular attention to alterations in patients' sleep quality to avoid development of a comorbid condition that could have been avoided with treatment of the sleep impairment.

A greater emphasis on maintaining a stable sleep/wake cycle and practicing adequate sleep hygiene would be beneficial for student populations, especially during times of increased stress such as mid-terms and finals. Sleep hygiene refers to behaviors that are believed to promote improved quantity and quality of sleep (Stepanski & Wyatt, 2003). Some common recommendations for improving sleep hygiene include maintaining consistent sleep and wake times, avoiding caffeine and other stimulants 4-6 hours before bedtime, avoiding naps, avoiding exercise before bed, along with creating a sleep environment that is quiet, dark, comfortable and absent of distractions (Stepanski &

Wyatt, 2003). Additionally, following an established pre-sleep ritual coupled with activities that promote relaxation have been shown to improve sleep quality (Stepanski & Wyatt, 2003). Considering that one cannot influence a genetic or developmental predisposition to depression, attention to daily behavioral patterns that can decrease vulnerability should be perceived as vital for maintaining homeostasis.

Future research in this area should investigate the role of sleep in longitudinal investigations which will elucidate the relationships among stress, sleep, and depression and allow for causal relationships to be inferred. While retrospective measures allow for analysis of large amounts of data often with little investment, prospective studies are important for research into the etiology of disease and would be helpful in this field of research (Clark & Doughty, 2008). Additionally, considering the data showing direct effects of clinically effective antidepressants on HPA axis function (Pariante, 2008), this area should be further investigated.

In closing, the current study supports the hypothesis that sleep plays a role in the relationship between stress and depression. Restorative sleep plays a moderating role in the stress/depression relationship, allowing an organism to adapt and decrease allostatic load. On the other hand, sleep impairments can be seen to exacerbate the relationship between stress and depression, increasing allostatic load, decreasing resiliency, and leaving the organism vulnerable to the development of a stress-related disorder such as depression. Lastly, sleep disruption should no longer be considered a stress-related outcome, but rather a biological stressor in itself that can lead to the development and maintenance of depression.

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Table 1

Bivariate Correlations (p Value and Number of Observations Below) between All Factors Measured: Perceived Stress, DASS_D, Sleep Quality, Duration, and Continuity

	PSS	DASS_D	PSQI	DURAT
DASS_D	0.65789 <.0001 367			
PSQI	0.50627 <.0001 334	0.50095 <.0001 328		
DURATION	-0.30204 <.0001 358	-0.18354 0.0006 348	-0.47426 <.0001 320	
CONT	0.18462 0.0003 375	0.22853 <.0001 365	0.41574 <.0001 338	-0.17152 0.0011 359

Figure 1

Three-Dimensional Depiction of the Two-Way Interaction between Sleep Quality and Perceived Stress on Depression, from ITALASSI

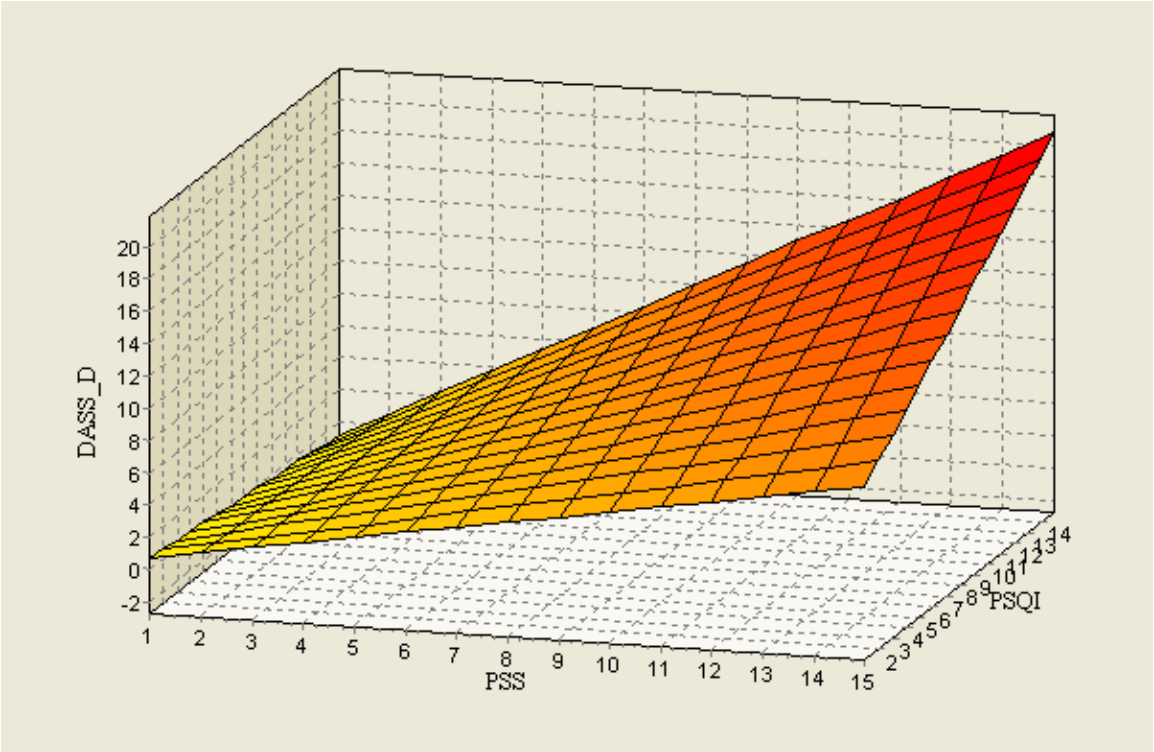
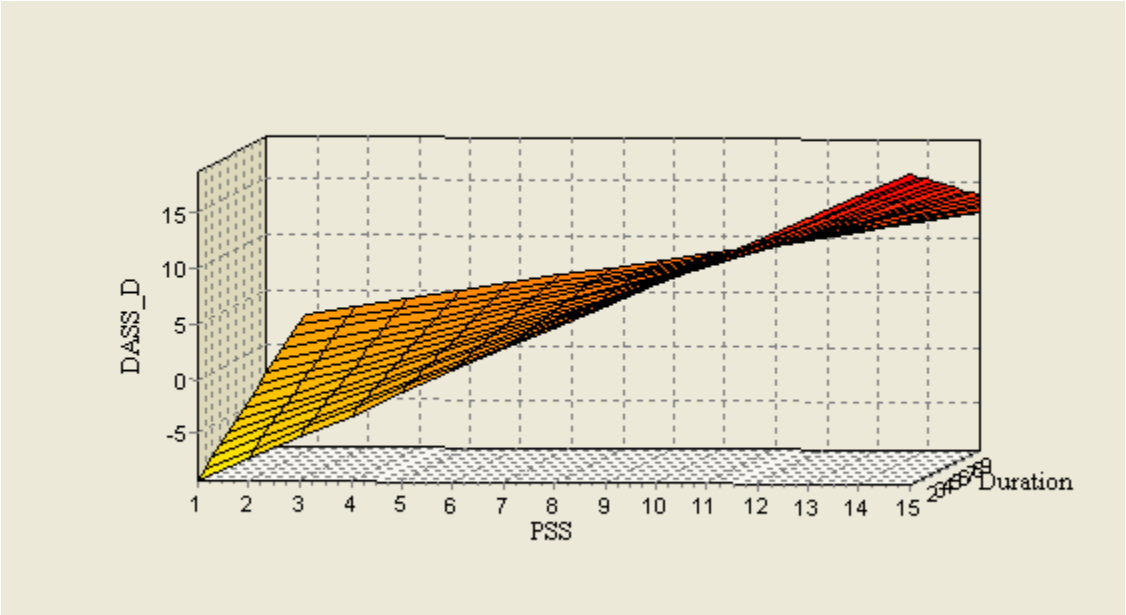


Figure 2

Three-Dimensional Depiction of the Two-Way Interaction between Sleep Duration and Perceived Stress on Depression, from ITALASSI



Appendix A

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be
different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

b) Wake up in the middle of the night or early morning

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

c) Have to get up to use the bathroom

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

d) Cannot breathe comfortably

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

e) Cough or snore loudly

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

f) Feel too cold

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

g) Feel too hot

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

h) Had bad dreams

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

i) Have pain

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

j) Other reason(s), please
describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you
have had . . .

a) Loud snoring

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

b) Long pauses between breaths while asleep

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

c) Legs twitching or jerking while you sleep

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

e) Other restlessness while you sleep; please
describe_____

_____

Not during the Less than Once or twice Three or more
past month_____ once a week_____ a week_____ times a week_____

Appendix B
Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly? **0 1 2 3 4**

2. In the last month, how often have you felt that you were unable to control the important things in your life? **0 1 2 3 4**

3. In the last month, how often have you felt nervous and "stressed"? **0 1 2 3 4**

4. In the last month, how often have you felt confident about your ability to handle your personal problems? **0 1 2 3 4**

5. In the last month, how often have you felt that things were going your way?..... **0 1 2 3 4**

6. In the last month, how often have you found that you could not cope with all the things that you had to do? **0 1 2 3 4**

7. In the last month, how often have you been able to control irritations in your life? **0 1 2 3 4**

8. In the last month, how often have you felt that you were on top of
9. things?..... **0 1 2 3 4**

9. In the last month, how often have you been angered because of things that were outside of your control? **0 1 2 3 4**

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? **0 1 2 3 4**

Appendix C

DASS 21

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3