Investigating the effect of sleep deprivation on hypothalamic-pituitary-adrenal-axis functioning and attentional biases to emotional information: an experimental study

by

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List of Acronyms

ACTH – Adrenocorticotropic hormone

ANOVA – Analysis of Variance

AUC – Area Under the Curve

AUCg – Area Under the Curve (ground)

CAR – Cortisol Awakening Response

CRH – Corticotropin-Releasing Hormone

ESS – Epworth Sleepiness Scale

GAD-7 – Generalized Anxiety Disorder Screener

GR – Glucocorticoid Receptor

HPA – Hypothalamic Pituitary Adrenal

ISI – Insomnia Severity Index

MEQ – Morningness-Eveningness Questionnaire

MS – milliseconds

NA – Negative Affect

PA – Positive Affect

PANAS – Positive and Negative Affect Scale

PERI-LES – Psychiatric Epidemiology Research Interview - Life Events Scale

PHQ-9 – Patient Health Questionnaire

PSS – Perceived Stress Scale

PSQI – Pittsburgh Sleep Quality Index

REM – Rapid Eye Movement

RT – Response Time

SCN – Suprachiasmatic Nucleus

SOL – Sleep Onset Latency

SWS – Slow Wave Sleep

TIB – Time in Bed

TSST – Trier Social Stress Test

TST – Total Sleep Time

WASO – Wake After Sleep Onset

%SE – Percent Sleep Efficiency

Abstract

OBJECTIVE: Sleep deprivation is associated with a number of negative health outcomes, such as stress-related disorders (e.g., depression and insomnia). However, the mechanisms by which sleep deprivation leads to poor health are unclear. Therefore, directly examining the consequences of sleep deprivation and how they may inform our understanding of stress-related disorders is a major public health concern. The primary aim of the current study was to examine the effect of total sleep deprivation (29 consecutive hours awake) on diurnal hypothalamic-pituitary-adrenal-axis (HPA-axis) and cognitive biases to emotional information, given their demonstrated link to stress-related disorders. Specifically, we investigated whether sleep deprivation was: 1) associated with cortisol reactivity to an acute laboratory stressor, 2) key to understanding the meaning and function of the cortisol awakening response, and 3) related to attentional biases to emotional stimuli. METHODS: Participants included 40 healthy young adults between the ages of 18 – 29. The current protocol included spending two nights in the laboratory: 1) during night one, participants underwent an adaptation night in order to acclimate to sleeping in a novel environment, and 2) during night two, participants were randomized into either a sleep deprivation condition or a control condition. Following the night two, all participants completed cognitive testing, online self-report questionnaires, and a laboratory stress protocol. Salivary cortisol was collected in the morning during the first hour after awakening and during the stress protocol. During the week prior to coming in to the laboratory, participants wore actigraphy devices and completed a sleep diary to assess their baseline sleep patterns. RESULTS: Our data indicated that there were significant group differences in cortisol following

the laboratory stressor, however, the findings were inconsistent with our original hypotheses (aim 1). Specifically, the results demonstrated that participants in the sleep deprivation condition had greater baseline (i.e., pre-stress) cortisol, but that it was participants in the control condition that showed greater cortisol reactivity to the stressor. Participants in a sleep-deprived condition instead had a blunted endocrine response to stress. Furthermore, our findings revealed that while participants in the control condition demonstrated a traditional rise and fall of cortisol following awakening, the participants in the sleep deprivation condition showed no increases in morning cortisol (i.e., no CAR). Finally, the data revealed that while controlling for insomnia symptoms, sleep deprivation was not associated with a greater negative bias. In contrast, sleep deprivation predicted a significantly reduced positive bias, but only among participants with low self-reported sleep difficulties (i.e., ISI scores). CONCLUSION: The current study was the first to use a carefully controlled sleep manipulation to examine whether sleep deprivation had a direct impact on HPA-axis and cognitive functioning. Our findings provided further support for the notion that acute sleep deprivation has an effect on cortisol under non-stressful conditions, but not necessarily under stressful conditions. Furthermore, acute sleep deprivation was also linked to a reduced attentional bias for positive information, but this association was moderated by sleep difficulties. Overall, this dissertation provides a broad investigation of the physiological and psychological consequences of sleep deprivation. The current findings have important implications for identifying potential targets for future examinations that may improve our understanding of the mechanisms by which sleep deprivation increases risk for stress-related disorders.

Chapter 1: Introduction

While individual sleep need varies widely from person to person, most sleep experts recommend 7 to 9 hours of sleep per night. Yet, in the United States, the average time slept on workdays is approximately 6.5 hours (National Sleep Foundation, 2013). Moreover, nearly 30% of adults sleep 6 or fewer hours per night (Krueger & Friedman, 2009). These rates are concerning as sleep deprivation is linked to a number of negative health outcomes (Grandner, Patel, Gehrman, Perlis, & Pack, 2010), such as depression (Grandner et al., 2010; Perlman, Johnson, & Mellman, 2006), hypertension (Gangwisch et al., 2006; Gottlieb et al., 2006), diabetes (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005), and early mortality (Gallicchio & Kalesan, 2009). However, the actual mechanisms by which sleep deprivation impacts health are relatively unknown. In this study we examine two possible mechanisms through which sleep deprivation may increase the risk for negative health outcomes: endocrine (i.e., hypothalamic-pituitary-adrenal axis) and cognitive functioning (i.e., attentional biases), given their established links with several similar health conditions (e.g., Mogg & Bradley, 2005; Pariante & Lightman, 2008). Specifically, using a carefully controlled experimental protocol, we examined the physiological (i.e., endocrine) and psychological (i.e., cognitive) consequences of total sleep deprivation (29 consecutive hours awake). This research may therefore have implications for identifying potential mechanisms by which sleep deprivation leads to poor health, in particular stress-related disorders (e.g., depression, insomnia).

The hypothalamic-pituitary-adrenal-axis (HPA-axis), or the neuroendocrine system primarily responsible for modulating physiological reactivity to stress, is closely related to

individual sleep patterns (see Balbo, Leproult, & Van Cauter, 2010 for recent review).

Specifically, shorter sleep duration has been consistently linked to atypical HPA-axis functioning. For example, short sleep is associated with greater diurnal cortisol (Kumari et al., 2009), an elevated cortisol awakening response (CAR; Räikkönen et al., 2010; Vargas & Lopez-Duran, 2014), and greater cortisol reactivity in response to psychosocial stress (Hatzinger et al., 2008). This is not surprising as increased HPA-axis activation may be necessary to maintain wakefulness and alertness among sleep-deprived individuals (Meerlo, Sgoifo, & Suchecki, 2008). Yet, few studies have involved the manipulation of sleep in controlled conditions, and thus it is not clear whether inadequate sleep actually leads to greater HPA-axis activation during the subsequent day. Addressing this question is important because it is possible that lower sleep duration and HPA-axis functioning are not causally related and are instead due to a third variable, such as high levels of stress (Sadeh & Gruber, 2002; Sadeh, Keinan, & Daon, 2004) or the presence of comorbid psychiatric symptoms (Ivanenko, Crabtree, Obrien, & Gozal, 2006). However, experimentally controlled sleep deprivation is associated with elevated *diurnal* cortisol (Leproult, Copinschi, Buxton, & Van Cauter, 1997; Treuer, Norman, & Armstrong, 2007; Vgontzas et al., 2001), and thus it is possible that sleep deprivation directly impacts other indices of diurnal HPA-axis functioning (i.e., stress reactivity, CAR) as well. Therefore, the first aim of the study was to experimentally examine the direct impact of total sleep deprivation on other indices of diurnal HPA-axis functioning, in particular, cortisol stress reactivity. This contribution is significant because it may identify sleep as a direct contributor to HPA-axis dysregulation, which has theoretical and practical implications for a variety of stress-related disorders linked to greater HPA-axis reactivity (e.g., depression and insomnia; Burke, Davis, Otte, & Mohr, 2005; Vgontzas et al., 2001).

Variability in sleep duration has also been linked to other relevant indices of the HPA-axis, such as the cortisol awakening response (CAR; Elder, Wetherell, Barclay, & Ellis, 2013). CAR is a sudden increase in cortisol that occurs immediately following awakening (Pruessner et al., 1997). Most investigators agree that CAR may reflect both a direct physiological response to awakening (or more specifically, the transition from sleep to awakening; Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007) and a by-product of cortisol's circadian rhythm (Angela Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Angela Clow, Hucklebridge, & Thorn, 2010). Atypical CAR has been linked to a number of clinical disorders (e.g. Fries, Dettenborn, & Kirschbaum, 2009), and some studies suggest that it may even be a biomarker for stress-related disorders (Vrshek-Schallhorn et al., 2013). Despite speculation regarding its underlying function, however, the biopsychosocial meaning of CAR is relatively unknown, and examinations using experimental methods are scarce. Therefore, the current study offers a unique opportunity to specifically test whether CAR is a direct response to awakening or instead a circadian-driven process. Specifically, if CAR is primarily a circadian-driven process, acute sleep deprivation will not significantly adjust the timing of CAR. In contrast, there would be an immediate shift (or in this case, elimination) in CAR, if CAR were instead a direct response to awakening. Thus, the second aim of the current study was to experimentally manipulate sleep in order to shed light on the meaning of CAR, which may also has implications for a number of stress-related disorders linked to atypical CAR (i.e., depression).

In addition to investigating the physiological (i.e., endocrine) consequences of sleep deprivation, we were also interested in examining the psychological (i.e., cognitive) effects. Sleep has a direct impact on cognitive processes, such as sustained attention (Drake et al., 2001) and memory consolidation (Stickgold, 2005). There is also growing evidence to support the

association between sleep and cognitive biases for emotional stimuli. Such that negative information is preferentially encoded into long-term memory if learning has occurred following a period of sleep, and not wakefulness (Hu, Stylos-Allan, & Walker, 2006; Lewis, Cairney, Manning, & Critchley, 2011; Payne & Kensinger, 2010; Payne, Chambers, & Kensinger, 2012; Payne, Stickgold, Swanberg, & Kensinger, 2008; Wagner, Gais, & Born, 2001). In contrast to research on emotional memory functioning, little is known about the impact of sleep and/or sleep deprivation on attentional biases to emotional information. However, parallel lines of research have demonstrated that insomnia is characterized by greater attentional biases to sleep-related information. Furthermore, like emotional memory biases (Wingenfeld, Terfehr, Meyer, Löwe, & Spitzer, 2012), attentional biases to emotional stimuli are characteristic of many forms of psychopathology (Mogg & Bradley, 2005). Gaining a more clear understanding of whether sleep deprivation potentially contributes to individual and group differences in attentional biases to emotional stimuli is thus an important next step. Taken together, the third and final aim of the current study focused on the direct impact of sleep deprivation on attentional biases to emotional information. While we specifically focus on the implications this may have for understanding the factors that contribute to the development and maintenance of insomnia, this research may also have implications for other stress-related disorders that are characterized by sleep problems and attentional biases to emotional cues (e.g., depression; Breslau, Roth, Rosenthal, & Andreski, 1996; Gotlib, Krasnoperova, Neubauer Yue, & Joormann, 2004).

1.1 The overall cost of acute and chronic sleep deprivation

Research over the past 45 years has broadly documented the array negative consequences related to acute and chronic sleep deprivation (Durmer & Dinges, 2005; Knutson, Spiegel, Penev, & Van Cauter, 2007; Orzeł-Gryglewska, 2010; Pilcher & Horne, 1996). For example, acute

sleep deprivation has been linked to a number of neurocognitive deficits, such as impaired executive functioning, reduced learning and memory consolidation, and increased risk for accidents (see Durmer & Dinges, 2005 for review). Acute sleep deprivation is also associated with excessive daytime sleepiness (Stepanski, Zorick, Roehrs, & Roth, 2000) and increased negative mood or irritability (Pilcher & Horne, 1996). The impact of long-term or chronic sleep deprivation is also significant. Many physiological, behavioral, and cognitive-affective systems become significantly impaired as a result of chronic sleep deprivation. For example, studies that have observed sleep-restricted human volunteers over the course of several days to weeks showed a strong link between sleep deprivation and a number of physiological consequences, such as alterations in glucose metabolism (Knutson et al., 2007), impaired immune function (Dinges, Douglas, Hamarman, Zaugg, & Kapoor, 1995), and dysregulation of the HPA-axis (Meerlo et al., 2008). Notably, animal models have confirmed that chronic sleep restriction is causally linked to reduced immune function, and consequently, increased cancer cell growth (Hakim et al., 2014). Chronic sleep loss is also broadly associated with the development and maintenance of psychopathology (Morin & Ware, 1996), and in particular, stress-related disorders, such as depression (Breslau et al., 1996).

There are a number of reasons why humans are sleep deprived or fail to acquire sufficient sleep, but most can be attributed to environmental (e.g., work schedule, life demands), psychological (e.g., insomnia, anxiety), and physical (e.g., chronic pain, sleep apnea) factors (Krueger & Friedman, 2009). While the reason behind sleep loss certainly play an important role, past research points to a fundamental truth about sleep loss, in that, independent of everything else, not getting sufficient sleep has severe consequences on your overall physical and psychological health, and therefore it is essential to further understand and address these links.

Namely, the public health impact of sleep deprivation is large, and continued research efforts on understanding the consequences of sleep deprivation, and how these consequences may be related to negative health outcomes, is critical. Therefore, the broad goal of the current study is to identify additional consequences of sleep deprivation (e.g., greater endocrine stress reactivity and attentional biases to emotional information), which, in particular, may be able to advance our understanding of the factors that contribute to the development and maintenance of stress-related disorders, such as depression and insomnia. However, it is important to note that sleep deprivation due to environmental or physical factors, or in the case of the current study, in a laboratory setting, may be qualitatively different from sleep deprivation obtained due to the presence of a psychological or sleep disorder. Therefore, any implications the current findings may have for psychopathology are limited to the effects of voluntarily imposed [acute] sleep deprivation and not sleep disruption that is part of a broader clinical syndrome.

1.2 The hypothalamic-pituitary-adrenal-axis and sleep

The hypothalamic-pituitary-adrenal-axis (HPA-axis) regulates a series of neuroendocrine responses to acute stressors that facilitate the mobilization of key adaptive physiological processes such as terminating digestive activity and maximizing glucose utilization (de Kloet, 1991; Johnson, Kamilaris, Chrousos, & Gold, 1992). Specifically, during stress, corticotropin-releasing hormone (CRH) is released from the hypothalamus, which subsequently triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the adrenal cortex, which produces and secretes glucocorticoids, the final byproduct of HPA-axis activation. Glucocorticoids, or cortisol in humans, are then responsible for initiating the negative feedback loop, thus shutting down the axis and release of CRH and ACTH (Gunnar & Quevedo, 2007; Tsigos & Chrousos, 2002). Under non-stressful conditions, the HPA-axis follows a

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circadian rhythm responsible for maintaining adaptive levels of stress hormones (see Figure 1). Specifically, glucocorticoids increase rapidly during the night, peak shortly after awakening (i.e., cortisol awakening response), and decline progressively throughout the day to reach their lowest levels around bedtime (Buckley & Schatzberg, 2005; Gunnar & Vazquez, 2001).

Studies have recently begun to identify biopsychosocial factors that may explain individual and group differences in HPA-axis functioning (Fries et al., 2009). For example, sleep plays a potentially important role in regulating the HPA-axis (Buckley & Schatzberg, 2005; Meerlo et al., 2008). In fact, the systematic link between sleep and *nocturnal* HPA-axis functioning has been relatively well documented (see Born & Fehm, 1997 for review). Specifically, nocturnal cortisol secretion fluctuates as a function of sleep activity. Slow wave sleep (SWS), which primarily occurs during the first part of the night, has an inhibitory effect on cortisol release, whereas nocturnal awakenings and REM sleep are associated with increased cortisol secretion (Born & Fehm, 1997; Born et al., 1986; Ekstedt, Åkerstedt, & Söderström, 2004; Spath-Schwalbe, Gofferje, Kern, Born, & Fehm, 1991). Furthermore, during post-deprivation recovery sleep, cortisol is negatively associated with the percentage of SWS (Vgontzas et al., 1999). Taken together, these studies provide support for the inhibitory role of SWS and excitatory role of REM-sleep on HPA-axis functioning, in particular, cortisol release.

While these findings support sleep's regulatory effect on HPA-axis functioning, cortisol has also been shown to fluctuate as a function of light exposure (Wehr, 1998). Therefore, it is possible that the suprachiasmatic nucleus (SCN), the brain's "internal clock", which is regulated by changes in light exposure (Meijer, Watanabe, Schaap, Albus, & Detari, 1998), potentially explains the link between sleep and diurnal cortisol fluctuations. We are unable to fully separate the effect of sleep on HPA-axis functioning from that of circadian processes since previous

studies have primarily examined the link between sleep and *nocturnal* cortisol release (Born & Fehm, 1997). Therefore, it is important to examine the impact of sleep on other indices of HPA-axis functioning, such as daytime cortisol and cortisol in response to psychosocial stress. Yet, much less is known about the regulatory effect of sleep on these other indices of HPA-axis functioning, and until recently (Goodin, Smith, Quinn, King, & McGuire, 2012; Kumari et al., 2009; Räikkönen et al., 2010), few studies have investigated sleep's role in explaining differences in these indices. Preliminary studies, however, have indicated that subjectively and objectively reported sleep parameters may predict individual differences in diurnal cortisol functioning. For example, in both children (El-Sheikh, Buckhalt, Keller, & Granger, 2008) and adults (Hsiao et al., 2010; Kumari et al., 2009), shorter sleep duration is associated with a flatter diurnal cortisol slope across the daytime. Thus, short sleep may result in greater evening cortisol activation, which potentially reflects sleep's role in modulating the HPA-axis throughout the 24-hour period. An important next step is to investigate the association between sleep and other daytime indices of HPA-axis functioning, in particular those that have been previously linked to negative health conditions, such as HPA-axis stress reactivity and the cortisol awakening response (Burke et al., 2005; Chida & Steptoe, 2009). This may allow us to gain a more complete understanding of the association between sleep and the HPA-axis.

1.3 Aim 1: Sleep deprivation and HPA-axis stress reactivity

Short sleep, defined as habitual sleep time of six hours or less, is a growing public health concern (Grandner et al., 2010). Specifically, short sleep is linked to a number of negative health outcomes, such as depression (Breslau et al., 1996; Perlman et al., 2006), hypertension (Gangwisch et al., 2006; Gottlieb et al., 2006), and diabetes (Spiegel et al., 2005). Growing research points to variability in neuroendocrine functioning, in particular the hypothalamic-

pituitary-adrenal-axis (HPA-axis), as a potential mechanism by which short sleep leads to poor health (Balbo et al., 2010; Meerlo et al., 2008).

The HPA-axis' primary function is to regulate physiological responses to stress (de Kloet, 1991; E. Johnson et al., 1992). HPA-axis stress reactivity is, however, also modulated by several individual (e.g., age, gender; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004) and contextual factors (e.g. time of day; Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004). Among these factors, sleep may also play a particularly critical role in modulating HPA-axis stress reactivity (Sgoifo et al., 2006). Several studies suggest that poor sleep is associated with atypical cortisol reactivity in response to psychosocial stress among both children (Hatzinger et al., 2008; Räikkönen et al., 2010) and adults (Wright, Valdimarsdottir, Erblich, & Bovbjerg, 2007). Specifically, poor self-reported sleep quality has been linked to elevated cortisol reactivity in response to a laboratory stress task (Goodin et al., 2012). Similarly, among children, lower objective sleep quality (e.g., lower sleep efficiency, more time spent in 'light' stages of sleep) predicted greater overall cortisol production in response to stress (Hatzinger et al., 2008; Räikkönen et al., 2010). Poor or insufficient sleep may increase adrenal sensitivity, and thus exacerbate cortisol production during acute stress. For example, following a 48h sleep deprivation protocol, sleep deprived rodents showed blunted ACTH compared to sleep control rats, whereas glucocorticoid (i.e., cortisol) production was not significantly different between the two groups (Sgoifo et al., 2006). Accordingly, under sleep-deprived conditions, less ACTH may be needed to signal the appropriate release of glucocorticoids in response to stress, which is consistent with a more sensitive HPA-axis. Yet, these previous findings are limited to rodent samples (Meerlo, Koehl, van der Borght, & Turek, 2002; Sgoifo et al., 2006), and do not explain

why other studies have reported a link between greater sleep difficulties and reduced glucocorticoid production in response to stress (e.g., Wright et al., 2007).

Among older children and adolescents (i.e., ages 10-17), greater self-reported sleep-wake behavior problems (e.g., prolonged sleep latency, poor sleep quality, and nightmares) were significantly associated with *blunted* peak cortisol following a stressor (Capaldi, Handweger, Richardson, & Stroud, 2005). Similar results were shown among healthy adult women, specifically, lower sleep efficiency was associated with blunted peak cortisol (Wright et al., 2007). Thus, an alternative explanation may be that sleep difficulties instead impair the HPA-axis' negative feedback process by increasing glucocorticoid receptor (GR) sensitivity. GRs are low-affinity receptors that are primarily activated during times of high cortisol production (e.g., stress or cortisol awakening response; Buckley & Schatzberg, 2005). However, if GR sensitivity is increased, cortisol will bind more readily to GRs and thus artificially shutting down the axis early (Balbo et al., 2010). These inconsistencies may also be attributed to methodological differences, such as age and sex of the sample (Kudielka et al., 2004; Kudielka & Kirschbaum, 2005), or how sleep disturbances were assessed (Capaldi et al., 2005; Pesonen et al., 2012; Wright et al., 2007). Taken together, these previously mixed results highlight our poor understanding of the relationship between sleep disturbances and HPA-axis stress reactivity.

Given the paucity of empirical research on this topic, it is important for future investigations, in particular those using experimental methods, to focus on the effect of sleep on HPA-axis *stress reactivity*. To date, no human studies have investigated the impact of sleep loss under controlled conditions; therefore, it is unknown whether sleep deprivation (i.e., acute sleep curtailment in a laboratory setting; Grandner et al., 2010) actually leads to differences in HPA-axis stress reactivity during the subsequent day. Accordingly, the current study explored the

association between total sleep deprivation (29 consecutive hours awake) and cortisol reactivity to a psychosocial stress task under controlled conditions. We hypothesized that sleep deprivation would be associated with greater cortisol in response to stress, given the demonstrated links between sleep disturbances and increased HPA-axis stress reactivity (Goodin et al., 2012; Hatzinger et al., 2008; Räikkönen et al., 2010) and sleep deprivation and increased adrenal sensitivity among non-human models (Meerlo et al., 2002; Sgoifo et al., 2006). This contribution is significant as it may identify sleep deprivation as a direct contributor to HPA-axis dysregulation, which has treatment implications for a variety of conditions linked to atypical HPA-axis reactivity (e.g., depression; Burke et al., 2005)

1.4 Aim 2: The cortisol awakening response: "response" to awakening or circadian processes?

There has been a proliferation of research using variability in CAR as an index of HPA-axis activity and as a biomarker of many disorders (e.g., depression; Vrshek-Schallhorn et al., 2013). Yet, despite its growing use in clinical research over the past two decades (Chida & Steptoe, 2009), there is a limited understanding of CAR's fundamental biopsychosocial function and meaning (Clow et al., 2010a; Fries et al., 2009). While CAR is commonly characterized as a *response* to the transition from sleep to awakening (e.g., Wilhelm et al., 2007), it remains unclear whether this transition is necessary for CAR to occur, or whether CAR can occur in the absence of awakening (i.e., after total sleep deprivation). Therefore, the second aim of the current study was to advance our understanding of CAR by experimentally testing whether CAR is observed in the absence of awakening.

The original and most common explanation of CAR is that it is an endocrine response to awakening, possibly due to the stress of awakening. Prior research suggests that the awakening

process, as well as factors that contribute to variability in the awakening process (e.g., time of day, Devine and Wolf, 2016), plays an important role in determining the timing and intensity of CAR. In fact, nocturnal profiles of plasma adrenocorticotropic hormone (ACTH) and cortisol have demonstrated an acute rise in hormone levels immediately following awakening (Born, Hansen, Marshall, Mölle, & Fehm, 1999; Wilhelm et al., 2007). The post-awakening rise, as well as the post-rise recovery, in HPA-axis hormones appears to be a deviation from the expected circadian pattern. Specifically, this rise and fall represents an abrupt break from the gradual increase and decrease in cortisol and ACTH observed during the night and day, respectively (Ranjit, Young, Raghunathan, & Kaplan, 2005). Therefore, CAR is arguably distinct (and superimposed) from the natural circadian rhythm of ACTH and cortisol (Wilhelm et al., 2007). Furthermore, there is evidence for a "flip-flop" switching off and on of particular cortical and sub-cortical brain regions during the transition to awakening. This switch is associated with an increase in adrenal sensitivity to ACTH, which is purportedly responsible for the post-awakening rise in cortisol (i.e., see Clow et al., 2010a for review).

Alternatively, CAR has also been conceptualized as part of a circadian process, and not simply an endocrine response to awakening (Clow et al., 2010a; Clow et al., 2010b). Diurnal (i.e., circadian) HPA-axis fluctuations, including CAR, are strongly driven by the suprachiasmatic nucleus (SCN), or the brain's internal "clock" (Buckley & Schatzberg, 2005; Clow et al., 2010b). Such that, as light exposure, which traditionally corresponds with the transition from sleep to awakening, provides excitatory input to the SCN, the SCN enhances adrenal sensitivity to ACTH and increases the release of cortisol (Clow et al., 2010a; Meijer et al., 1998). Thus, CAR may also be an SCN-mediated regulatory process that enables our ability

to maintain homeostatic levels of morning cortisol, which coincides, likely functionally, with the expected time of awakening.

These two conceptualizations of CAR are not antithetical, in that both may influence CAR: the process of awakening and circadian pressure from central drive excitatory input. For example, studies also suggest that pre- and post-awakening endocrine levels are modulated by a number of factors related to the awakening process, such as timing (e.g., early vs. late) and mode (e.g., spontaneous vs. planned). For example, participants who wake up "early" show greater post-awakening ACTH and cortisol production relative to those who wake up "late" (Born et al., 1999; Edwards, Evans, Hucklebridge, & Clow, 2001). Born and colleagues (1999) also demonstrated that having prior knowledge of what time awakening would occur was associated with a gradual increase in plasma ACTH during the hour prior to awakening, and therefore, those who had a surprise or spontaneous awakening showed a greater and more acute post-awakening ACTH response. Taken together, these studies suggest that circadian processes associated with the expected waking time, and the acute process of an unexpected awakening, can govern CAR.

CAR also varies as a function of multiple individual (e.g., age, sex; Kudielka & Kirschbaum, 2003; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000) and contextual factors (e.g., stressful events, day of week; Chida & Steptoe, 2009; Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004), suggesting it can also reflect processes beyond basic neuroendocrine functioning. Among these factors, sleep has been linked to individual and group differences in CAR (see Elder et al., 2013 for a recent review). Growing evidence suggests that a number of different sleep parameters may be linked to individual differences in CAR. For example, CAR has been found to vary as a function of sleep quality (Kumari et al., 2009), awakening time (Edwards et al., 2001; Federenko et al., 2004) and nocturnal awakenings (Hatzinger et al., 2008).

Likewise, preliminary evidence supports the link between shorter sleep time and elevated CAR (Kumari et al., 2009; Vargas & Lopez-Duran, 2014). However, these results have been mixed (e.g., Zhang et al., 2011), and difficult to interpret given the variability in how CAR is assessed (e.g., slope, r^2 change, AUC_g; Clow, Thorn, Evans, & Hucklebridge, 2004). In a recent study (Vargas & Lopez-Duran, 2014), we provided additional evidence for the link between lower total sleep time (TST) and elevated CAR (Figure 2). Specifically, lower TST was associated with lower cortisol at awakening and greater CAR. The impact of TST on cortisol at awakening may reflect the natural rise in cortisol across the sleep period (Steiger, 2002), such that those with lower TST likely awoke during an earlier phase of the pre-awakening cortisol rise. Taken together, the current study controlled for a number of these factors (e.g., baseline sleep, stress, psychiatric symptoms, and biological sex), given their demonstrated link to differences in CAR.

While prior research has consistently demonstrated that the variability in the transition from sleep to awakening *can* impact CAR (Born et al., 1999; Wilhelm et al., 2007), there is a paucity of experimental research investigating whether this transition is *necessary* to produce CAR (i.e., can it occur in the absence of a sleep-to-wake transition). In fact, few studies have actually involved the manipulation of sleep or wake in controlled conditions, and these studies have been limited to napping conditions or failed to formally operationalize CAR (e.g., Devine and Wolf, 2016; Monk et al., 1997). Therefore, using a carefully controlled experimental protocol, the current study examined whether CAR was present among individuals undergoing a night of total sleep deprivation. By manipulating sleep, this study may help clarify whether CAR is influenced by the HPA-axis' circadian drive independently of the awakening process, or rather, a response that is fully dependent on awakening.

1.5 Aim 3: Sleep deprivation and attentional biases to emotional information

While the prevalence rate of insomnia varies across reports (5 -50%), studies suggest that approximately one-third of the adult population have a current history of at least one nocturnal insomnia symptom (i.e., difficulty initiating or maintaining sleep or non-restorative sleep; Morin & Jarrin, 2013). The medical and socioeconomic impact of insomnia is vast and a major public health concern (Mai & Buysse, 2008). Therefore, efforts to identify and understand the factors that contribute to the development and maintenance of insomnia are critical. One factor that studies suggest may be involved in the development and maintenance of insomnia is attentional biases to sleep-related stimuli (see Harris et al., 2015 for review). However, what is less clear is how individuals with insomnia develop these biases, and whether these biases precede (and thus contribute to the development of) the disorder, or whether they develop as a function of the disorder (and then maintain it). One relatively recent study demonstrated that sleeplessness or poor sleep quality can elicit these kinds of attentional biases (Spiegelhalder, Espie, & Riemann, 2009). However, no study has examined whether sleep loss in controlled conditions (i.e., sleep deprivation) can directly create these attentional biases. Furthermore, past research has been limited to the investigation of sleep-related attentional biases, and therefore, it is unclear whether insomnia is also associated with attentional biases to emotional information, in general, such as in other stress-related disorders (i.e., depression and anxiety; Gotlib et al., 2004; Mogg & Bradley, 2005). The final aim of the current study was to investigate whether experimental sleep deprivation can create attentional biases to emotional information, and whether current insomnia symptoms moderate this effect.

The impact of sleep disturbance and insomnia symptoms on attentional processes has been widely examined (Killgore, 2010). Namely, sleep disturbances and/or insomnia symptoms

have been linked to impaired attentional capacity and functioning. For example, people who report greater insomnia symptoms show more difficulties with memory (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012), and vigilance (Altena, Van Der Werf, Strijers, & Van Someren, 2008). However, few studies have directly examined the association between sleep disturbances, particularly sleep deprivation, and attentional biases to emotional stimuli. This is concerning given that parallel lines of research support the link between insomnia and attentional biases, specifically for sleep-related stimuli (Harris et al., 2015). Unlike other attentional processes (e.g., vigilance), which are likely a consequence of the associated sleep disturbances, sleep related attentional biases may actually contribute to the development and maintenance of insomnia. In fact, cognitive models of insomnia (i.e., Espie, Broomfield, MacMahon, Macphee, & Taylor, 2006; Espie, 2002; Harvey, 2002) characterize the disorder by excessive focus on sleep-related information. According to these models, a sleep-related attentional bias may have a bidirectional relationship with insomnia (Espie et al., 2006; Harris et al., 2015). While individual variability in attentional biases to sleep-related stimuli poses as a potential vulnerability factor to developing insomnia, the development of sleep disturbances may increase these biases, which in turn, may perpetuate the disorder.

While these models provide important speculation regarding the potential pathway(s) by which insomnia and sleep-related attentional biases are bidirectionally linked, these pathways have yet to be directly examined, and thus the nature of this relationship is still unclear. Research investigating the link between insomnia and sleep-related attentional biases, however, has been cross-sectional (see Harris et al., 2015 for review), and except for one study that reported no attentional biases (Sagaspe et al., 2006), this link has yet to be examined in controlled conditions (i.e., sleep deprivation). For example, it is possible that the insomnia-

related sleep disturbances or sleep loss may play a critical role in modulating attention to emotionally relevant information given that the physiological structures responsible for modulating attentional capacity to emotionally relevant information (and among individuals with insomnia symptoms, this would include sleep-related stimuli) are impacted by sleep. Specifically, sleep deprivation is associated with greater amygdala activation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), which facilitates the processing of emotional relevant information, particularly negative stimuli. Thus, one potential explanation is that increased amygdala activation is one mechanism by which sleep loss creates attentional biases for negative information. Therefore, the final aim of the current study is to investigate the direct link between sleep deprivation and attentional biases using a carefully controlled experimental protocol.

Another limitation of previous research is that past studies have been limited to the examination of sleep-related attentional biases (Harris et al., 2015), and therefore, whether insomnia is associated with attentional biases to emotional information, more broadly, is unclear. Attentional biases to emotional information has been previously linked to various other stress-related disorders, particularly depression (e.g., Gotlib et al., 2004; Joormann & Gotlib, 2007; Joormann, Talbot, & Gotlib, 2007) and anxiety (Cisler & Koster, 2010). Specifically, studies have shown that individuals with depression and anxiety display significant attentional biases for negative stimuli during laboratory tasks (Bar-Haim, Lamy, Lee, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Gotlib & Neubauer, 2000). For example, compared to 'healthy' controls, currently depressed participants also demonstrated an attentional bias to negative (sad faces), but not positive (happy faces) or anxiety-relevant stimuli (angry faces; Gotlib et al., 2004). Similar findings have been reported among groups with a history of anxiety (Cisler & Koster, 2010). These results suggest that cognitive biases to negative information may be a common

vulnerability factor among stress-related disorders. However, past studies have yet to examine whether these broader attentional biases to emotional information are also characteristic of insomnia. This is surprising given the diagnostic overlap and high comorbidity rates with both depression and anxiety disorders (Buysse et al., 2008; Johnson, Roth, & Breslau, 2006). Therefore, the current study also examined the direct impact of sleep deprivation on attentional biases to emotional information, broadly, and not necessarily specific to sleep-related stimuli.

Taken together, the current study examined whether sleep deprivation had a direct impact on attentional biases to emotional information, as this may have implications for understanding the link between insomnia and attentional biases. Notably, we conducted the current experiment among a non-clinical sample (i.e., no history of clinical insomnia or other psychopathology). By examining the link between acute sleep deprivation and attentional biases among a sample with no history of insomnia, we can reasonably infer that any differences in attentional biases are a function of our sleep manipulation and not pre-existing biases that are a function of having a history of insomnia. Therefore, any significant differences between groups would suggest that attentional biases were a *consequence* of acute sleep deprivation. However, even among a sample of healthy young adults, who have no history of clinical insomnia, there is considerable individual variability in sleep difficulties or insomnia *symptoms* (Ohayon, 2002). As stated above, insomnia [symptoms] and attentional biases likely have a bidirectional relationship (Espie et al., 2006; Harris et al., 2015), and therefore, even mild or subthreshold insomnia levels may be associated with greater sleep-related attentional biases. Therefore, studies investigating the impact of experimental sleep deprivation on attentional biases must also account for any attentional biases that may be a consequence of pre-existing sleep difficulties. To this end, we predicted that sleep deprivation would be associated with a greater bias for negative information

and a reduced bias for positive information, but that these biases would be moderated by current sleep difficulties, such that those participants with greater sleep difficulties would have reduced biases. Specifically, these findings would suggest that the effect of acute sleep deprivation would be greater among participants with no current history of sleep difficulties (i.e., insomnia symptoms), and blunted among participants with [mild] pre-existing sleep difficulties.

1.6 Summary of Aims and Hypotheses

The goal of this dissertation was to investigate the physiological and psychological consequences of acute sleep deprivation. The hope is that these findings will have important implications for research on stress-related disorders (i.e., depression and insomnia), and this may potentially lead to the identification of targets for prevention and intervention. To this end, we used experimental methods to systematically examine the impact of total sleep deprivation on diurnal HPA-axis functioning (i.e., cortisol stress reactivity and CAR) and attentional biases to emotional information among a sample of healthy young adults. In summary, we addressed three important aims:

1. To investigate the link between acute sleep deprivation and our ability to physiologically cope with stress. Specifically, we examined the effect of total sleep deprivation on HPA-axis reactivity to a standardized laboratory stress task. We hypothesized the participants in the sleep deprivation condition will have a heightened cortisol response to a psychosocial stressor compared to participants in the control condition.

2. To advance our understanding of the cortisol awakening response by experimentally testing whether CAR is observed in the absence of awakening. If CAR is primarily a circadian-driven process, it is unlikely that acute sleep deprivation would significantly adjust the timing of CAR. In contrast, there would be an immediate shift (or in this case,

elimination) in CAR, if CAR was instead a direct response to awakening. We hypothesized that CAR is primarily a response to awakening, and therefore, predicted that participants in the sleep deprivation condition will have a significantly blunted CAR.

3. To examine the direct association between acute sleep deprivation and cognitive biases to emotional information. To this end, our goal was to determine whether experimental sleep deprivation can create attentional biases to emotional information. We predicted that sleep deprivation would be associated with a greater bias for negative information and a lesser bias for positive information, but that these biases would be moderated by baseline sleep difficulties, such that those participants with greater sleep difficulties would have blunted responses to the attention task.

Chapter 2: Methods

2.1 Participants

Participants included 45 young adults (22 females; M_{age} = 22.6, SD_{age} = 3.1) recruited from the local community. Participants were recruited through online and printed advertisements placed in local businesses and community centers seeking ''healthy'' young adults for sleep study. Recruitment strategies included: a) community advertisements in local community centers and businesses, b) posters and flyers placed throughout the University of Michigan campus, c) online advertisement at various websites (e.g., Google text ads, Craigslist, Facebook ads, AnnArbor.com), and d) the MICHR clinical studies homepage (www.umclinicalstudies.org). Participants will be ineligible for participation if they 1) are pregnant, 2) are currently taking any medication that impacts endocrine functioning, 3) have a chronic medical condition (e.g., cancer, lupus, diabetes), 4) have a chronic endocrine disorder (e.g., Cushing's syndrome, Addison's disease), or 5) have been previously diagnosed with a psychiatric or sleep disorder. Also, participants who are unable to maintain a regular sleep cycle during the week prior to the overnight visits (e.g., shift worker) were excluded from the study. Five participants (2 females; M_{age} = 21.8, SD_{age} = 3.4) dropped out before completing all the parts of the study, and were therefore excluded from the current analyses. The final sample included 40 participants (20 females; M_{age} = 22.7, SD_{age} = 3.1). The majority of participants identified as Caucasian (57.5%) and in college (75%; undergraduate and graduate students). The remaining sample was composed of 20.0% African American, 12.5% Asian American, and 2.5 Biracial. 12.5% of the

sample identified as Hispanic. The Institutional Review Board at the University of Michigan approved the study, and participants completed written informed consent.

2.2 Procedures

This protocol included three laboratory visits: a baseline visit and two follow-up overnight weekend visits (see Figure 3). In addition, participants wore an actigraphy watch and completed a sleep diary during the week between the baseline visit and the first follow-up visit. The study was conducted at the Michigan Psychoneuroendocrinology Affective Laboratory (Michigan PAL) located at the University of Michigan Department of Psychology.

Baseline laboratory visit. During the baseline visit, each participant completed a series of questionnaires about their sleep habits. Specifically, these questionnaires assessed general sleep patterns (Pittsburgh Sleep Quality Index; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), daytime sleepiness (Epworth Sleepiness Scale; Johns, 1991), circadian preference (Morningness-Eveningness Questionnaire; Horne & Ostberg, 1975), and insomnia symptoms (Insomnia Severity Index; Morin, 1993). Following the baseline visit, participants wore an actigraphy device (Actiwatch-2; Philips Respironics, Andover, MA, USA) on their wrist for approximately seven days (range = 2-11 days). The actigraph is a widely used method for objectively assessing daily sleep/wake patterns (Sadeh, Sharkey, & Carskadon, 1994). In addition, each day participants were asked to complete a brief online sleep diary (Consensus Sleep Diary; Carney et al., 2012). While the aims of the current study were to determine the impact of sleep deprivation using experimental methods, it is important to systematically control for pre-existing differences in baseline sleep patterns. Participants were also instructed to maintain a regular sleep/wake schedule (i.e., 7-8h of sleep per night; morning waking time between 06:00-09:00) and abstain from napping during the subsequent week.

Overnight laboratory visits. Approximately one week after the baseline visit, each participant returned to the lab on two consecutive weekend nights. During the first night, or the adaptation night, participants were instructed to arrive to the lab at approximately 22:00. Beginning at 0:00 (midnight), all participants were instructed to be in bed with the lights off (lights out). The adaptation night served to familiarize the participants with sleeping in a novel environment. Participants were instructed to get out of bed (lights on) immediately after awakening; however, any participants still sleeping at 08:00 were awoken by the research staff. Participants were given a maximum 8h sleep opportunity time. Participants were allowed to go home following the adaptation night, and instructed to return to the lab the subsequent night at 22:00. During the second night, or the experimental night, participants were randomized into either the sleep deprivation group or control group. During the experimental night, participants assigned to the control group were given another 8h sleep opportunity time (lights out = 0:00; lights on = 08:00). Participants assigned to the sleep deprivation group underwent a night of total sleep deprivation (29 consecutive hours awake). Participants in the sleep deprivation group had access to the Internet, music, and DVD player, and were otherwise allowed to move about the laboratory under the supervision of the research staff. Participants were only allowed in rooms that were video-monitored or occupied by research staff. Staff members continuously monitored participants throughout the night in order to ensure wakefulness. Participants continued to wear actigraphs throughout both overnight laboratory visits.

2.3 Endocrine Assessment

Cortisol awakening response. Cortisol is commonly used as the index for HPA-axis functioning, with increased cortisol levels representing increased activity in the HPA-axis. Saliva collection was used as the method of obtaining cortisol. Specifically, during the

experimental visit, participants were asked to provide six saliva samples in the morning by spitting into a Salivette (Sarstedt, Nümbrecht, Germany). Trained laboratory staff collected all saliva samples in order to ensure accuracy. The first sample was obtained immediately upon the participant's final awakening. For example, participants whose final awakening was before 08:00 began saliva collection at the time of their final awakening. The following five samples were taken approximately at 30, 45, 60, 120, and 150 minutes after awakening. For participants in the sleep deprivation condition, cortisol collection began at 08:00. Participants were asked to refrain from brushing their teeth and any vigorous activity (e.g., exercise) until the end of the morning sample collection phase.

Laboratory Stress Task. In order to produce an endocrine stress response, we used a modified version of the Trier Social Stress Task (TSST; Kirschbaum, Pirke, & Hellhammer, 1993). All participants participated in the TSST between approximately 11:00 - 13:00. The TSST consisted of a brief preparation period, a socially-evaluated speech, an arithmetic task in front of two trained judges, and a 45-minute regulation phase. This task has been shown to reliably activate the HPA-axis in previous controlled laboratory experiments (Kudielka, Hellhammer, & Kirschbaum, 2007). During the regulation phase, each participant watched a neutral film (i.e., National Geographic). Salivary cortisol was also collected during the laboratory stress protocol as a marker of HPA-axis stress reactivity. Saliva samples were collected before, during, and after the TSST. A total of 11 saliva samples per participant were obtained throughout the protocol. Specifically, the first sample was obtained approximately 10 minutes before the beginning of the speech preparation period. The second sample was taken at the beginning of the speech preparation period. The following nine samples were obtained 10

(end of speech task), 15 (end of arithmetic task), 20, 25, 30, 35, 40, 50, and 60 minutes after the beginning of the TSST (see Figure 4).

Endocrine Assay. Laboratory staff were instructed to store all saliva samples in a freezer within 1h of collection. Samples were stored at −20°C until assayed and were centrifuged for 15 minutes prior to assay. Samples were assayed in duplicates and averaged using a commercial Enzyme Linked Immunosorbent Assay (ELISA) kit (Salimetrics LLC, Carlsbad, CA, USA). To avoid inter-assay variability all samples from the same participant were assayed in the same batch. Duplicates varying more than 15% were re-assayed. The inter-assay and intra-assay coefficients of variability were 11.8 (High = 11.3, Low = 12.4) and 4.8, respectively. Saliva samples were analyzed for cortisol at the Core Assay Facility of the University of Michigan's Department of Psychology.

2.4 Measures

Objective baseline sleep patterns. Following the baseline visit, participants were asked to wear an actigraphy device (Actiwatch-2; Philips Respironics, Andover, MA, USA) on their wrist for approximately seven days. The actigraph is a widely used method for objectively assessing daily sleep/wake patterns (Sadeh et al., 1994). The Actiwatch-2 is a reliable and relatively unobtrusive tool. In addition, each day the participants were asked to complete a brief online sleep diary (Consensus Sleep Diary; Carney et al., 2012). The Consensus Sleep Diary, developed by a committee of sleep research experts at the Pittsburgh Assessment Conference, is a nine-item self-report measure used to collect information about daily sleep patterns. The diary asked participants to report each day the time they attempted to fall asleep, how long it took them to fall asleep, the number and duration of awakenings experienced, and their final time of awakening. Participants completed sleep diaries on each day they wore the Actiwatch-2. Sleep

diaries were only used to verify that the actigraph data was valid. Actigraphy and sleep diary data were used to estimate each participant's average sleep data from the week prior to the overnight laboratory visit, and therefore, control for factors that may have influenced a participant's response to the sleep deprivation protocol (e.g., naps, average sleep duration, etc.). The following sleep parameters were used as covariates for the current analyses: total sleep time (TST), sleep efficiency (%SE), sleep onset latency (SOL; how long it took them to initiate sleep, in minutes), wake after sleep onset (WASO; sum of their nocturnal awakenings, in minutes), and nocturnal awakenings (awakenings; total number of times they woke up at night).

General sleep quality. The Pittsburgh Sleep Quality Index (PSQI; (Buysse et al., 1989) was used to assess general sleep quality over the past month. The PSQI is a widely used self-report instrument with good reliability and validity in both healthy (Grandner, Kripke, Yoon, & Youngstedt, 2006) and clinical samples ($\alpha > 0.80$ across groups; Carpenter & Andrykowski, 1998). The PSQI has since been translated and used across a number of different countries and populations (Doi et al., 2000; Tsai et al., 2005). The PSQI was administered during the baseline visit and during the adaptation night.

Insomnia symptoms. The Insomnia Severity Index (ISI; Morin, 1993) was used to assess perceived sleep difficulties or current insomnia symptoms (i.e., past two weeks). The ISI is a 7-item, self-report instrument with good reliability and validity, and positively correlated with clinician-rated insomnia diagnoses (Bastien, Vallières, & Morin, 2001). Total scores on the full 7-item scale range from 0 – 28. This measure demonstrated good internal consistency in the current sample ($\alpha = 0.81$) and good one-week test-retest reliability (Pearson's $r = 0.82$). The ISI was administered during the baseline visit and during the adaptation night.

Daytime sleepiness. The Epworth Sleepiness Scale (ESS; Johns, 1991) was used to assess subjective daytime sleepiness. The ESS is a well-validated and widely used self-report measure of general daytime sleepiness. Specifically, the ESS is an 8-item questionnaire that examines the likelihood a participant would fall asleep in different situations (e.g., sitting and reading, watching TV, or in a car, while stopped for a few minutes in traffic). The ESS has previously demonstrated good psychometric properties (Johns, 1992), such as test-retest reliability (r=0.82) and internal consistency (α=0.88). The ESS in our current sample also showed good internal consistency (α=0.79). The ESS has demonstrated to be a useful tool for distinguishing between normal subjects and patients with sleep disorders, such as insomnia, obstructive sleep apnea, and narcolepsy (Johns, 1991; Ustinov et al., 2010). The ESS was administered during the baseline visit and during the adaptation night.

Circadian preference. The Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976) was used to assess circadian preference typology. Circadian preference typology is a dimensional construct that describes a person's relative position between two extremes, morning chronotype and evening chronotype. High scores on the MEQ are consistent with a morning chronotype, and suggest the individual has a relative preference to go to bed early and wake up early. Whereas low scores on the MEQ are consistent with an evening chronotype, and suggest the individual has a relative preference to go to bed late and wake up late (Adan, Archer, & Hidalgo, 2012). The MEQ in our current sample also showed good internal consistency (α=0.76). The MEQ was administered during the baseline visit.

Self-reported mood. Participants also completed additional self-report measures to control for depressive symptoms, anxiety, and affect. The Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001) was used to assess current depressive symptomatology (i.e.,

during the past two weeks). The PHQ-9 is a 9-item, self-report instrument with excellent

reliability and validity (Kroenke et al., 2001), and can be used as a screening tool for depression

(Williams et al., 2005). Total scores on the full 9-item scale range from $0 - 27$. The Generalized

Anxiety Disorder Screener (GAD-7) was used to assess current anxiety and worry. The GAD-7

is a 7-item, self-report instrument with good reliability and validity (Spitzer, Kroenke, Williams,

& Löwe, 2006), and can be used as a screening tool for generalized anxiety (Löwe et al., 2008).

Total scores on the full 7-item scale range from $0 - 21$. Finally, the Positive and Negative Affect

Scale (PANAS; Watson, Clark, & Tellegen, 1988) was used to assess positive and negative

affect. The PHQ-9 and the GAD-7 were completed during the adaptation night (prior to going to

sleep), and the PANAS was completed the morning of the TSST within one hour of awakening

(for the control group) or between 08:00-09:00 (for the sleep-deprived group).

Self-reported stress. The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein,

1983) was used to assess current perceived stress, whereas an adapted version of the Psychiatric

Epidemiology Research Interview - Life Events Scale (PERI-LES; Dohrenwend, Krassnoff, &

Askenasy, 1978) was used to assess exposure to stressful life events during the past six months.

The PSS is a widely used self-report instrument with adequate reliability and validity in both

healthy (Roberti, Harrington, & Storch, 2006) and clinical samples (Hewitt, Flett, & Mosher,

1992). The PSS was administered during the adaptation visit. The original PERI-LES is a 102-

item self-report scale, in which participants are asked to rate on a 7-point Likert scale whether a

particular life event occurred during that past 6 months and to what extent the event was

"undesirable" (e.g., 7 = "very undesirable"; 1 = "not at all undesirable"). The types of events

included in the scale varied across multiple domains (e.g., interpersonal, economic, and

occupational). The PERI-LES was administered during the adaptation visit and was modified to ask about only events that occurred during the previous week (i.e., baseline week).

Attentional biases. In order to assess for attentional biases for emotional information, we used a modified version of the Dot Probe Task. This task is a widely used measure of attentional processes (MacLeod, Mathews, & Tata, 1986), and a similar version has been previously used in clinical research (Gotlib et al., 2004; Joormann & Gotlib, 2007; Joormann et al., 2007) . In this task, each participant was shown a fixation mark in the middle of a computer screen. This mark was followed by a brief (1,500ms) presentation of two images placed in different halves of the screen (right and left). This was followed by the presentation of a dot that appeared on one half of the screen. The participant was simply asked to wait until he or she saw the dot and then identify the location (i.e., right or left side of screen) of the dot using buttons on a control box. Participant's answers were assessed for accuracy and response time. The dot probe task was conducted using E-Prime 2.0 software (Psychology Software Tools) on an IBM-compatible computer and the images were presented on a 17-in Dell computer monitor. The size of the images were approximately 9 X 10 cm when presented on the monitor, and were symmetrically place on each half of the screen. The image pairs presented in this task consisted of a set of 10 faces, each expressing happy, sad, and neutral emotions. The images were selected from the NimStim Face Stimulus Set validated by the Research Network on Early Experience and Brain Development (Tottenham, Borscheid, Ellertsen, Marcus, & Nelson, 2002). The faces used were of mixed-race, adult human faces, and included an equal number of male and female faces. For each presentation, one face was always an 'emotional face' (happy or sad) and the other face was always a 'neutral' face. The order (whether positive or negative) and location (whether right or left side of the screen) of the images were selected randomly. After completing

10 practice trials, a total of 96 trials were presented to each participant (48 happy and 48 sad). The Dot Probe Task was completed during the morning after the experimental night, between approximately 11:00-12:00.

Attentional bias scores were computed using average response times (RT) for each valence [positive or negative] and condition [probe in same location as emotional face (i.e., match) or probe in different location as emotional face (i.e., no match)] pair. To minimize outliers, RTs that were less than 100 ms (i.e., anticipation errors) were excluded from the analyses. Similarly, RTs that were greater than 1,000 ms were also excluded because the delays were too long to reflect genuine responses, and were likely lapses in concentration (Joormann & Gotlib, 2007). Excluded trails accounted for less than 1% of the overall data. Positive and negative bias scores were estimated by taking the difference between the average RT when the probe was in a different location as the emotional face (i.e., no match) and the RT time when the probe was in the same location as the emotional face (i.e., match).

Positive bias score = AvgRT[positive-no match] - AvgRT[positive-match]

Negative bias score = AvgRT[negative-no match] - AvgRT[negative-match]

To this end, higher negative or positive bias scores indicate faster response times when the dot is behind a negative or positive image, respectively, whereas they indicate slower response times when the dot is behind a neutral image. A greater bias score, therefore, reflects a participant has a greater tendency to allocate his or her attention and/or more difficulty disengaging their attention to emotional stimuli. Bias scores that were beyond two SDs from the mean were excluded from our primary analyses.

2.5 Statistical Analyses

Aim 1. We used multiple adjusted random effects growth curve models via SPSS MIXED to examine the impact of our experimental protocol on cortisol stress reactivity. Specifically, we examined the effect on pre-stress, baseline cortisol (intercept) and cortisol reactivity (slope) from baseline. We used mixed modeling as opposed to repeated measures ANOVA in order to model the correct covariate structure of the interrelated repeated measures data (Gueorguieva & Krystal, 2004; Hruschka, Kohrt, & Worthman, 2005). We used mixed modeling as opposed to basic examinations of Area Under the Curve (AUC) because it allows for better characterization of patterns of activation and thus can be more sensitive to subtle differences in cortisol reactivity (Lopez-Duran, Mayer, & Abelson, 2014). All models included intercept and reactivity slopes as random effects within subjects. Winsorization procedures were used to exclude significant outliers (top 2%). To correct for skewness, cortisol data were transformed using a Box-Cox transformation (λ=-0.33; Miller & Plessow, 2013). All other skewed data were log-transformed. Continuous variables were mean-centered to ease interpretation. Age, menstrual cycle, oral contraceptive use, actigraphy data, self-report sleep/circadian measures, and other covariates (e.g., depressive symptoms) were first examined via independent unadjusted models to determine their effect on cortisol stress reactivity.

Aim 2. We also used multiple adjusted random effects growth curve models via SPSS MIXED to examine the impact of our experimental protocol on the cortisol trajectory from awakening (i.e., CAR). Specifically, we examined the effect on awakening cortisol (intercept) and cortisol reactivity (slope) from awakening. All models included intercept and reactivity slopes as random effects within subjects. Cortisol and other skewed variables were log-transformed to attain normality. However, model estimates and standard errors were back-

transformed in our figures to aid interpretability of the results (Jorgensen & Pedersen, 1998). Age, menstrual cycle, oral contraceptive use, actigraphy data, self-report sleep/circadian measures, and other covariates (e.g., depressive symptoms) were first examined via independent unadjusted models to determine their effect on CAR.

    Aim 3. We used linear regression models via SPSS MIXED to examine the impact of our experimental protocol on attentional biases to positive and negative stimuli. Specifically, positive and negative bias scores were entered as our dependent variables in separate linear regressions. Our first step included a number of relevant covariates (i.e., insomnia symptoms, average total sleep time, and perceived stress) as independent predictors. Our second and final step included group status (i.e., sleep deprivation vs. controls) as an independent variable. All skewed data were log-transformed. Continuous variables were mean-centered to ease interpretation. Age, gender, actigraphy data, self-report sleep/circadian measures, and other covariates (e.g., depressive symptoms) were first examined via independent unadjusted models to determine whether there were any significant differences between groups.

Chapter 3: Results

3.1 Descriptive statistics

Table 1 presents Pearson's *r* correlations between all continuous independent variables. As expected, the correlations among a number of sleep parameters were relatively strong. For example, greater self-reported sleep difficulties or insomnia symptoms (ISI) were significantly correlated with a lower overall sleep quality (PSQI), $r = 0.72$, and average total sleep time (TST), $r = -0.40$. Greater average TST was associated with greater sleep efficiency (%SE), $r = 0.43$. Moreover, greater PSQI scores were correlated with greater daytime sleepiness, $r = 0.45$. Also not surprisingly, there was a significant correlation between age and circadian preference typology (MEQ), $r = 0.41$, such that being older was associated with a relative likelihood for bring a morning chronotype (i.e., natural preference to go to bed earlier and wake up earlier). Table 1 also revealed that greater depressive symptoms were strongly correlated with poor sleep assessed via both the ISI, $r = 0.72$, and the PSQI, $r = 0.51$, and greater anxiety symptoms, $r = 0.56$. Interestingly, in the current sample, stressful life events (PERI-LES) were very strongly correlated with greater actigraphy reported sleep onset latency (SOL), $r = 0.75$.

Table 2 presents group means and standard deviations of all study variables (except cortisol). There were significant group differences for a number of variables. Specifically, relative to the control group, the sleep-deprived group reported significantly greater perceived stress (PSS), $F = 6.16$, $p = 0.02$. Furthermore, compared to participants in the control condition, participants in the sleep deprivation condition reported a lower average time in bed (TIB) during

the week prior to the experimental visit, $F = 6.94$, $p = 0.01$, which likely led to a lower average TST, $F = 5.67$, $p = 0.02$. Not surprisingly, the sleep-deprived group reported greater negative affect, $F = 10.9$, $p < 0.01$, and lower positive affect, $F = 5.00$, $p = 0.03$, the morning after the experimental night compared to the control group. There were no significant differences in habitual caffeine use between groups, $F = 0.704$, $p > 0.20$. Group mean comparisons of the raw, untransformed data indicated that there were also significant group differences in morning cortisol (Table 3). The control group had significantly greater cortisol at 30, $F = 4.94$, $p = 0.03$, 45, $F = 9.68$, $p < 0.01$, and 60, $F = 8.79$, $p < 0.01$, minutes post-awakening compared to the sleep-deprived group, but no differences were observed at awakening (i.e., 08:00), $F = 0.31$, $p > 0.20$ (Figure 6). Based on independent t-tests, there was also a significant group difference in pre-stress baseline cortisol (-10 min prior to TSST), $F = 4.76$, $p = 0.035$, but no differences in cortisol at any other time point (Figure 7). Finally, while there was not a group difference in the percent of females on birth control, $F = 0.78$, $p > 0.20$, the majority of females in the sample ($n=12$; 60%) were currently using at least one form of contraceptive.

3.2 Modeling CAR and HPA-axis stress reactivity

To determine whether linear or quadratic models were better fits to the endocrine data, we first computed unconditional models (i.e., no predictor variables) across both groups with cortisol as the outcome variable. Modeling morning cortisol alone suggested that cortisol increased linearly from awakening (time = 0), time $b = -.0009$, $t(39) = -2.62$, $p = .01$, but there was a significant deceleration of this increase over time, time^2 $b = -.00002$, $t(158) = -4.2$, $p < .001$, reflecting the overall expected rise and fall of the cortisol awakening response (linear model AIC = -52.8 vs. quadratic model AIC = -46.5). Modeling cortisol stress reactivity alone suggested that cortisol increased linearly from baseline (time = -10 min pre-stress), time $b = .065$,

$t(259) = 13.4$, $p < .001$, but there was a significant deceleration of this increase over time, time^2 b = -.0007, $t(358) = -12.3$, $p < .001$, reflecting the expected rise and fall of cortisol in response to a psychosocial stressor (linear model AIC = 1034.2 vs. quadratic model AIC = 926.0).

3.3 Aim 1: Sleep deprivation and HPA-axis stress reactivity

Unadjusted group effect predicting cortisol stress reactivity. We first computed an unadjusted model to examine the effect of condition (i.e., sleep deprivation versus control group) on cortisol stress reactivity. Results from our unadjusted model indicated significant group differences in cortisol stress reactivity. Specifically, compared to participants in the control condition, participants in the sleep deprivation condition had greater baseline cortisol (i.e., pre-stress cortisol), group $b = .727$, $t(45) = 2.20$, $p = .03$, yet a blunted cortisol response, group x time $b = -.026$, $t(251) = -2.66$, $p < .01$, group x time^2 $b = .0003$, $t(357) = 2.52$, $p = .01$. These data suggest that, despite having lower cortisol at baseline, it was the participants in the control condition that had a greater cortisol response to the TSST compared to those in the sleep deprivation condition (Figure 8).

Covariates and adjusted group effect predicting cortisol stress reactivity. We next examined whether the impact of group remained significant while controlling for biological sex, habitual caffeine use, perceived stress (PSS), average total sleep time (TST), and positive (PA) and negative (NA) affect. We included sex and caffeine use in the subsequent analyses given the previously observed link between these variables and cortisol stress reactivity (Al'Absi et al., 1998; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka & Kirschbaum, 2005; Lane, Adcock, Williams, & Kuhn, 1990; Lane, 2002). We also included the remaining covariates in the subsequent analysis given the significant group differences mentioned above. No other covariates were included in the final analyses. PSS and TST were not significantly

associated with cortisol reactivity while controlling for the group effect, and thus, due to the small sample size, we did not include PSS and TST in the final analyses. We controlled for effects of sex/caffeine use and PA/NA in two separate models. In our final adjusted models, our results confirmed that participants in the sleep deprivation condition had greater baseline cortisol, yet a blunted cortisol stress response, compared to participants in the control condition (Table 4). Sex, habitual caffeine use, PA, and NA were also independently associated with cortisol stress reactivity. Specifically, compared to females, males showed a greater cortisol response to the TSST, sex x time $b = .016$, $t(231) = 3.28$, $p < .01$, sex x $time^2$ $b = -.0002$, $t(355) = -3.23$, $p < .01$ (Figure 9). Similarly, compared to participants who reported no caffeine use, caffeine users showed a greater cortisol response to the TSST, caffeine x time $b = .019$, $t(231) = 3.21$, $p < .01$, caffeine x $time^2$ $b = -.0002$, $t(355) = -3.52$, $p < .001$. Greater PA and NA were also associated with an elevated cortisol stress response, PA x time $b = .095$, $t(221) = 2.21$, $p = .03$, PA x $time^2$ $b = -.001$, $t(337) = -2.40$, $p = .02$, NA x time $b = .212$, $t(221) = 2.47$, $p = .01$, NA x $time^2$ $b = -.003$, $t(337) = -3.15$, $p < .01$. See Table 4 for all parameter estimates in our final adjusted model.

3.4 Aim 2: The cortisol awakening response: "response" to awakening or circadian processes?

Unadjusted covariates predicting CAR. To determine which covariates should be included in our primary analyses, we conducted unadjusted random-effects models to examine the independent effect of each covariate on the cortisol awakening response (CAR) during the experimental visit. Each covariate was included as a fixed effect in independent regression models (Table 5). Notably, only Morningness-Eveningness Questionnaire (MEQ) scores were significantly associated with CAR. Specifically, lower MEQ scores were associated with a steeper cortisol increase from awakening, time $b = -0.0003$, $t(193) = -2.62$, $p < .01$, and a

significant deceleration of this increase over time, time^2 b = 0.000001, $t(158)$ = 2.06, p = .04.

These findings suggest that relative "evening types" (i.e., lower MEQ score; natural preference to go to bed later and wake up later) had a greater CAR when compared to relative "morning types" (i.e., greater MEQ; natural preference to go to bed earlier and wake up earlier). All other covariates were unrelated to CAR (see Table 5), and therefore, only MEQ was included as a covariate in our final model.

Unadjusted and adjusted group effect predicting CAR. Results from our unadjusted model indicated significant group differences in CAR. Specifically, compared to the control group, the sleep-deprived group had a blunted CAR, group x time b = -.006, $t(193)$ = -3.94, p < .001, group x time^2 b = .00005, $t(158)$ = 5.23, p < .001. These data suggest that the sleep-deprived group did not demonstrate the expected increase in morning cortisol, time b = -.0009, $t(193)$ = -0.89, p > .20, time^2 b = .000004, $t(159)$ = 0.57, p > .20. We computed additional models adjusting for the effects of perceived stress (PSS) and baseline TST (TST) given the observed group differences in PSS and TST. The group effect remained significant after controlling for PSS and TST, group x time b = -.008, $t(174)$ = -4.21, p < .001, group x time^2 b = .00005, $t(143)$ = 5.24, p < .001. Our results also remained significant when MEQ was entered into the model, time b = -.005, $t(191)$ = -3.60, p < .001, time^2 b = .00004, $t(156)$ = 4.97, p < .001. Furthermore, the effect of MEQ on CAR also remained significant while controlling for the group effect, time b = -.0002, $t(191)$ = -2.22, p = .03, suggesting the effect of MEQ on CAR is independent of any possible group differences in morningness-eveningness. Please refer to Table 6 for all model estimates.

3.5 Aim 3: Sleep deprivation and attentional biases to emotional information

      Unadjusted covariates predicting attentional bias. To determine which covariates should be included in our primary analyses, we first conducted separate regression models to determine the independent effect of each covariate on attentional biases to positive and negative stimuli. Each covariate was included as a fixed effect in independent regression models predicting negative bias scores and positive bias scores. Notably, no covariates were significantly associated with negative or positive bias scores, and therefore, they were not included in our final regression models. Given the previously demonstrated association between insomnia and attentional biases (Harris et al., 2015), our final analyses also examined the independent and combined effect of insomnia symptoms. Please see Table 7 for all covariate model estimates.

      Insomnia symptoms and group effect predicting negative bias. We then conducted a linear regression to determine the independent and combined effects of sleep deprivation and insomnia symptoms on attentional biases to negative stimuli. Results revealed that the main effect of sleep deprivation was not associated with negative bias scores while controlling for insomnia symptoms, $b = -3.42$, $t(35) = -0.47$, $p > .20$. Insomnia symptoms were also not independently associated with negative bias scores, $b = -1.56$, $t(35) = -0.21$, $p > .20$. The interaction effect was also not significant, $b = -14.93$, $t(34) = -1.03$, $p > .20$, suggesting that insomnia symptoms did not moderate the relationship between sleep deprivation and attentional biases to negative stimuli (Table 8).

      Insomnia symptoms and group effect predicting positive bias. We next examined the impact of sleep deprivation and insomnia symptoms on attentional biases to positive stimuli. Sleep deprivation was not independently associated with differences in positive bias scores while

controlling for insomnia symptoms, $b = -8.56$, $t(35) = -1.63$, $p = .11$. However, the main effect of insomnia symptoms was marginally significant, $b = 10.22$, $t(35) = 1.94$, $p = .06$. The data indicated that participants with greater self-reported insomnia symptoms, or sleep difficulties, were also more likely to have greater positive bias scores. Furthermore, while the interaction effect was not statistically significant, $b = 15.66$, $t(34) = 1.52$, $p = .14$, the interaction model did reveal a dynamic relationship between condition and ISI scores, and their combined effect on positive bias scores. Specifically, according to results from the interaction model (Table 8), participants with no current history of sleep difficulties (i.e., low ISI scores) had significantly lower positive bias scores, but only among those participants in the sleep deprivation condition, $b = 17.87$, $t(34) = 2.47$, $p = .02$ (Figure 10). In contrast, there was no association between sleep difficulties and positive bias scores among participants in the control condition, $b = 2.21$, $t(34) = 0.30$, $p > .20$. Pairwise comparisons also confirmed that among participants with no current history of sleep difficulties (i.e., low ISI scores), there was a significant group mean difference in positive bias scores, $p = .03$. Specifically, participants in the sleep deprivation condition had significantly lower positive biases scores compared to those in the control condition (Figure 10).

Chapter 4: Discussion

4.1 Aim 1: Sleep deprivation and HPA-axis stress reactivity

The negative health consequences of sleep deprivation are a growing public health concern. For example, it is believed that sleep deprivation adversely affects how animals, including humans, cope with stress (Killgore et al., 2008; McEwen, 2006). Studies suggest that sleep deprivation is associated with differences in HPA-axis functioning (Meerlo et al., 2002; Meerlo et al., 2008). Yet, few studies have examined whether sleep deprivation impacts HPA-axis functioning in controlled conditions (Leproult et al., 1997), and no study has specifically examined whether experimental sleep deprivation directly impacts HPA-axis functioning under stress conditions. The first aim of the current study was to investigate whether total sleep deprivation (29 consecutive hours awake) led to differences in HPA-axis reactivity during a psychosocial stress task. We predicted that sleep deprivation would be associated with greater HPA-axis or cortisol reactivity to the laboratory stressor, given that sleep disturbances have previously been linked to increased adrenal sensitivity and/or impaired glucocorticoid feedback regulation (Leproult et al 1997, Meerlo et al., 2008). While our data suggest there were significant group differences in cortisol following the laboratory stressor, the findings were inconsistent with our hypotheses. Specifically, the results demonstrated that participants in the sleep deprivation condition had greater baseline (i.e., pre-stress) cortisol and a blunted cortisol response to the stressor.

This is the first study to examine the relationship between sleep deprivation and HPA-axis stress reactivity in humans under controlled conditions. Consistent with previous studies (i.e., Leproult et al., 1997), sleep deprivation was associated with elevated baseline (i.e., pre-stress) cortisol, and thus, further supports that acute sleep loss can alter the diurnal cortisol slope among healthy, young adults. Circadian HPA-axis functioning, and subsequently cortisol release, is mediated by the suprachiasmatic nucleus (SCN; Clow et al., 2010a). SCN-mediated regulatory processes allow us to maintain homeostatic levels of cortisol throughout the day (Clow et al., 2010b). While the circadian rhythm of most physiological systems is relatively stable (Czeisler, Duffy, & Shanahan, 1999) and resistant to changes or shifts in the environment (e.g., jet lag; Winget et al., 1984), studies indicate the endocrine hormones, in particular, HPA-axis hormones may be affected by acute changes in the environment. Specifically, individual and contextual factors, such as acute stress and sleep loss may alter diurnal cortisol rhythms (Chida & Steptoe, 2009; Elder et al., 2013). Greater cortisol activation following acute sleep deprivation may serve a number of physiological processes. Namely, elevated cortisol may be a coping response to the stress of being acutely sleep-deprived. An increase in cortisol is a natural response, and enables our peripheral systems to cope with increased demands (i.e., stress; Gunnar & Quevedo, 2007). Alternatively, greater diurnal cortisol following acute sleep deprivation may reflect impairments in the HPA-axis' ability to regulate negative glucocorticoid feedback (Meerlo et al., 2008). The HPA-axis is equipped with a self-regulatory negative feedback system in order to prevent the overproduction of stress hormones. As cortisol begins to increasingly bind to low-affinity glucocorticoid receptors, signals are sent to the hypothalamus and anterior pituitary to shut down the production of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), and thus stopping the release of cortisol (Buckley &

Schatzberg, 2005). Acute sleep deprivation, whether as a direct result of sleep loss or the stress associated with being sleep deprived, may impair this self-regulatory process, which would in turn lead to greater cortisol production.

In contrast to our hypotheses, sleep deprivation was not associated with greater cortisol *reactivity* to an acute psychosocial stressor. Our findings instead suggested that participants in a sleep-deprived condition had blunted physiological responses to stress. Specifically, participants in the control condition had a significantly greater cortisol response to the TSST compared to those in the sleep deprivation condition. Although this effect remained significant even while statistically controlling for the group differences in baseline (i.e., pre-stress) cortisol, it is possible that these differences in baseline levels had an impact in the intensity of the stress response. Under stressful conditions, glucocorticoids (i.e., cortisol) initially bind to high-affinity mineralocorticoid receptors (MRs). Once MRs have been sufficiently saturated, cortisol begins to bind to glucocorticoid receptors (GRs), which then initiate the self-regulatory feedback system to shutdown the HPA-axis (Buckley & Schatzberg, 2005; Gunnar & Quevedo, 2007). If high baseline cortisol was therefore interpreted as the residual effects of a stress response to being acutely sleep-deprived, that would mean a number of MRs were being occupied that otherwise would be vacant. Consequently, cortisol produced by the TSST (among those in the sleep deprivation condition) would bind to GRs more quickly, and thus shutdown the axis much sooner (creating an overall blunted response). The current findings may suggest that participants in the sleep deprivation condition are physiologically responding to an acute stressor (i.e., TSST) that is superimposed on another stressor (i.e., sleep deprivation), thus creating an artificially blunted cortisol response to the acute stressor.

Furthermore, while the TSST is a widely used and reliable protocol for producing an endocrine stress response, the TSST and other similar laboratory stressors occur in a controlled setting, and results vary by a number of individual and contextual factors (Kudielka et al., 2007). Unlike exogenous hormonal administration or the cortisol awakening response (CAR), cortisol output following the TSST is relatively moderate (Schmidt-Reinwald et al., 1999). It is possible that in these controlled laboratory settings there is a relative 'ceiling' on the amount of cortisol that can be produced. Taken together, a combination of high starting values and a 'ceiling effect' may explain why participants in the sleep deprivation condition demonstrated blunted cortisol stress reactivity. Notably, our sample consisted of relatively healthy young adults, and therefore, these factors may not be as relevant among clinical samples or other developmental groups, as studies suggest variability in cortisol (both diurnal and in response to stress) is greater and more unpredictable among clinical samples (Burke et al., 2005; Young, Abelson, & Cameron, 2004). Therefore, the cortisol 'ceiling' among clinical samples may be higher (e.g., depression) and thus, the relative opportunity to see whether sleep deprivation is associated with greater cortisol production in response to stress may be different. Future studies with alternative population (e.g., clinical samples) are thus critical for advancing our understanding of the link between sleep deprivation and HPA-axis stress reactivity.

The current study also demonstrated a significant difference in cortisol stress reactivity by biological sex and habitual caffeine use. Specifically, our findings revealed greater cortisol responses to the TSST among males. This is consistent with previous reports suggesting greater cortisol responses to laboratory stress tasks among males, in particular, young men (Kudielka & Kirschbaum, 2005). These differences may be due to the influence sex hormones have on endocrine stress reactivity (see Kudielka et al., 2007 for review). One seminal study

demonstrated that women in the luteal phase of their menstrual cycle has comparable cortisol stress responses to men, however, women in the follicular phase or those taking oral contraceptives had significantly lower cortisol responses (Kirschbaum et al., 1999). Hormonal contraceptive use is therefore likely contributing to the lower cortisol responses among females, given that 60% of females in our sample reported current contraceptive use. Alternatively, the sex differences in cortisol stress reactivity may be a function of the nature of the stress task (i.e., TSST). While males typically respond more strongly to achievement/evaluation-based stressors (such as the TSST), women typically respond more strongly to social or interpersonal-based stress tasks (see Stroud, Salovey, & Epel, 2002). Similarly, there was a significant relationship between habitual caffeine use and a greater overall cortisol response to the TSST. This is consistent with previous literature indicating that caffeine use, including habitual caffeine use, is positively linked to greater autonomic and endocrine responses to stress (Al'Absi et al., 1998; Lane et al., 1990; Lane, 2002). Taken together, these findings further support the notion that future studies investigating the individual and contextual factors impacting HPA-axis stress reactivity should account for these increasingly more established impact of biological sex and habitual caffeine use on cortisol responses to stress.

Positive and negative affect were also independently associated with variability in cortisol reactivity. Specifically, greater positive (PA) and negative affect (NA), as measured via the positive and negative affect scale (PANAS; Watson et al., 1988), were each associated with greater cortisol responses to the TSST. The positive relationship between greater PA and cortisol reactivity is not surprising, given that the control group reported significantly greater PA and cortisol reactivity. Therefore, the significant relationship between greater PA and an elevated cortisol response may simply be a proxy for their shared link to the control group, and

does not necessarily suggest that individuals with overall greater PA experience the TSST as more stressful (at least, physiologically). Alternatively, the association between greater NA and an elevated cortisol stress response may reflect a more genuine relationship that is independent of our experimental manipulation. It is possible that an elevated negative mood state may increase the participants' cognitive bias to negative information during the stress task (Beevers & Carver, 2003). Consequently, these participants (with greater NA) may have experienced the TSST as more stressful, which in turn led to a greater cortisol response. This makes sense given that cognitive processes, such as coping and controllability (Abelson, Khan, Liberzon, Erickson, & Young, 2008), mediate the intensity of the endocrine stress response. However, these conclusions are speculative, and future studies should use methodology that carefully examines the potential mechanistic role affect and mood have in explaining the link between sleep deprivation and cortisol stress reactivity. Furthermore, the current study assessed PA and NA in the morning, several hours prior to the stressor, and therefore affect immediately before or during the stressor may be more strongly associated with cortisol reactivity.

4.2 Aim 2: The cortisol awakening response: "response" to awakening or circadian processes?

The acute increase in cortisol following awakening has been previously conceptualized as an endocrine *response* to awakening (Born et al., 1999; Wilhelm et al., 2007; Devine & Wolf, 2016). However, there is evidence that CAR may be influenced by circadian input (Clow et al., 2010a; Clow et al., 2010b), which may be independent of the awakening process. The second aim of the current study was to investigate whether a CAR could be identified in the absence of the transition from sleep to wake (i.e., total sleep deprivation). We found significant group differences in CAR between participants in a sleep-deprived condition and a control condition.

While the control group demonstrated a traditional rise and fall of cortisol during the first two hours after awakening, the sleep deprivation group showed blunted cortisol in the morning and no significant increases from baseline (i.e., no CAR).

This is the first study to examine the possibility that circadian-driven processes that are not dependent on a response to awakening may influence CAR. SCN-mediated regulatory processes modulate HPA-axis functioning (Kalsbeek, Spek, & Lei, 2012; Nader, Chrousos, & Kino, 2010), and consequently the release of cortisol. These regulatory processes allow us to maintain homeostatic levels of cortisol throughout the day, including in the morning (Clow et al., 2010b). As mentioned above, the circadian rhythm of most human biological systems is relatively stable (Czeisler et al., 1999), and often resistant to changes or shifts in the environment (e.g., jet lag; Winget et al., 1984). Therefore, if CAR was primarily a circadian-driven process, it is unlikely that one night of sleep deprivation would significantly adjust the adrenal gland's internal clock and subsequently the timing of CAR. In contrast, you may expect to see an immediate shift (or in this case, elimination) in CAR, if CAR was instead a direct response to awakening. Total sleep deprivation is an ideal manipulation, as it removes the transition from sleep to awakening, and allows us to attribute any significant increases in morning cortisol (i.e., CAR) to circadian-driven processes. The only other study that has assessed morning cortisol after total sleep deprivation pre-dates our formal conceptualization of CAR, but also failed to find a clear CAR among sleep-deprived participants (e.g., Monk et al., 1997). They observed a rise and fall of cortisol during the awakening period, however such rise was gradual (under 20% increase) and likely reflected the general circadian pattern as opposed to the sharp inflection expected in CAR (Ranjit et al., 2005). Likewise we did not find evidence for CAR in the

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absence of awakening, suggesting that if circadian-driven processes influence CAR, they are only activated when awakening occurs or is anticipated (e.g., Born et al., 1999).

Although our results suggest that awakening is necessary for CAR to occur, it is unclear what aspect(s) of awakening may be modulating CAR. For example, CAR may be an endogenous response to awakening. The transition from sleep to wake marks a distinct switch in a number of physiological processes, in which a number of biological systems are being simultaneously turned off and on (such as increased adrenal sensitivity; Clow et al., 2010a; Clow et al., 2010b). Among other things, this switch enables our brain to transition from a state of unconsciousness to a state of full alertness (Balkin, Braun, & Wesensten, 2002). What is unclear, however, is whether post-awakening cortisol release (i.e., CAR) is responsible for activating and maintaining the transition to wakefulness, or instead responsible for the down-regulation of this transition. Increased adrenal sensitivity following awakening, which leads to greater cortisol release, increases the opportunity for cortisol to bind to low-affinity, peripheral glucocorticoid receptors (Gunnar & Quevedo, 2007; Gunnar & Vazquez, 2001). As cortisol binds to these glucocorticoid receptors, it may have contrasting effects, as it may: 1) stimulate cells responsible for the mobilization of energy stores throughout the body, or instead down-regulate the transition to wakefulness by initiating the HPA-axis' negative feedback once a certain number of glucocorticoids (i.e., cortisol) bind to glucocorticoid receptors (Gunnar & Quevedo, 2007). Alternatively, the intensity and timing of CAR may be related to third variables, such as stress (Sadeh & Gruber, 2002; Sadeh et al., 2004), sleep architecture (Devine & Wolf, 2016), or the presence of comorbid psychiatric symptoms (Ivanenko et al., 2006), that modulate the sleep-to-wake transition. Future investigations should focus on advancing our understanding the

underlying meaning and function of CAR, including the endogenous and exogenous factors that modulate the release of cortisol following awakening.

We also found that circadian preference typology, as assessed via the Morningness-Eveningness Questionnaire (MEQ), was associated with differences in CAR. Circadian typology is a dimensional construct that describes a person's relative position between two extremes, morning chronotype and evening chronotype. Morning chronotypes have a relative preference to go to bed early and wake up early, whereas evening chronotypes have a relative preference to go to bed late and wake up late (Adan et al., 2012). According to our results, a greater tendency for a morning chronotype (i.e., greater MEQ), participants demonstrated a more blunted CAR. These results were observed across both groups. While these findings appear to be inconsistent with previous research suggesting a greater CAR among morning chronotypes (Kudielka, Federenko, Hellhammer, & Wüst, 2006; Randler & Schaal, 2010), it is important to note that these prior studies did not standardize sleep and/or time of awakening across participants. These studies instead examined the association between chronotype and CAR in the context of habitual sleep patterns. It is possible that, in the current study, evening chronotypes may be waking up earlier than their habitual wake time, and therefore the awakening is experienced as more "stressful", resulting in a greater CAR. The effect of MEQ on CAR remained significant in our adjusted model, which suggests that this effect was independent of any possible group differences in circadian typology.

4.3 Aim 3: Sleep deprivation and attentional biases to emotional information

The prevalence and impact of insomnia is a major public health concern (Mai & Buysse, 2008). Continued research efforts to identify the factors that contribute to the development and maintenance of insomnia are critical. One factor that has consistently been linked to insomnia

has been attentional biases to sleep-related information. Specifically, studies have consistently

demonstrated that individuals with insomnia have a greater tendency to focus their attention to

sleep-related stimuli compared to non-sleep-related stimuli (Harris et al., 2015). However,

whether attentional biases are a vulnerability marker of insomnia has yet to be empirically tested.

Alternatively, attentional biases may be a consequence of insomnia or the sleep deficits it

produces. To this end, no study has examined sleep in controlled conditions (e.g., experimental

sleep deprivation) to determine whether sleep loss can create the observed attentional biases.

Furthermore, the insomnia literature has been limited to investigating attentional biases for *sleep-*

related information (see Harris et al., 2015 for review), and no studies have observed the

relationship between insomnia or sleep difficulties and attentional biases to emotional

information, more broadly. Attentional biases for emotional information have been consistently

linked to other stress-related disorders (i.e., depression and anxiety; Mogg & Bradley, 2005), and

therefore, it is possible that these biases also exist among people with insomnia or sleep

difficulties. Taken together, the final aim of the current study was to investigate the direct

impact of sleep deprivation on attentional biases for emotional information (i.e., negative and

positive images). In contrast to our original hypotheses, our results revealed that the independent

and combined effects of acute sleep deprivation and current sleep difficulties (i.e., ISI scores)

were not significantly associated with differences in attentional biases for negative information.

In contrast, acute sleep deprivation predicted a significantly reduced positive bias, but only

among participants with no sleep difficulties (low ISI scores.)

While controlling for current self-reported sleep difficulties (i.e., ISI scores), there was no

effect of sleep deprivation on attentional biases for negative stimuli. The interaction with sleep

difficulties was also not significant. Acute sleep loss did not increase the tendency for

participants to focus their attention on negative images relative to neutral images. In fact, participants across both conditions demonstrated, on average, a non-negative bias to the dot probe task (i.e., greater attention to neutral stimuli over negative stimuli). Previous studies have demonstrated that insomnia and sleep difficulties, including sleeplessness (Spiegelhalder et al., 2009), are associated with attentional biases for sleep related stimuli, which can be considered 'negative' stimuli for people with a history of insomnia [symptoms]. Therefore the sleep-attention link may be specific to sleep-related stimuli, and does not necessarily generalize to negative stimuli, more broadly. While these null results suggest that acute sleep loss does not impact attentional biases to negative stimuli, it may still be possible that they reflect a vulnerability marker of a clinical disorder (rather than a consequence of sleep loss). In fact, one study observed attentional biases to negative stimuli among a sample of adolescent girls at-risk for depression (i.e., at least one parent with a history of depression), which further supports that attentional biases precede the onset of psychopathology (Joormann et al., 2007). Alternatively, attentional biases to negative information may be a consequence of the syndrome or the disease process, and not simply a function of the disturbance or loss in sleep. This is an important distinction, given that sleep deprivation due to environmental factors (including voluntarily imposed sleep deprivation in a laboratory setting) may be fundamentally different from sleep disruption that is part of a broader clinical syndrome (as in depression or insomnia).

The main effect of sleep deprivation on attentional biases to positive information was also not supported. Strictly speaking, acute sleep loss did not have a significant impact on participants' tendency to focus on positive stimuli relative to neutral stimuli. Our findings, however, demonstrated that there was a trend-level ($p = 0.06$) main effect of self-reported sleep difficulties on positive bias scores. Specifically, greater ISI scores were associated with greater

positive bias scores, or participants with greater sleep difficulties had a greater tendency to attend to positive images relative to neutral images. Indeed, interpreting the main effect of sleep difficulties is not as meaningful in the context of a clear experimental manipulation (i.e., 50% of the sample has not slept in 26+ hours), and therefore, the interaction effects were also observed.

The interaction between condition and self-reported sleep difficulties predicting positive bias scores was not significant. While the interaction term was not statistically significant, the results from our interaction model did reveal a dynamic relationship between condition, sleep difficulties, and their interactive effect on attentional biases to positive stimuli. Specifically, according to our final model, participants in the sleep deprivation condition had a significantly lower positive bias score (lower and negative scores indicating a tendency to attend to neutral images over positive images) compared to the participants in the control condition, but this was only true among those participants with no pre-existing sleep difficulties (i.e., low ISI scores). In contrast, participants in the sleep deprivation condition who reported having a current history of (mild) sleep difficulties did not have a similarly reduced positive bias (Figure 10). Mean comparisons also indicated that among those participants with no current history of sleep difficulties, there was a significant group difference in positive bias scores. Participants in the sleep deprivation condition had lower (and significantly more negative) positive biases scores compared to their counterparts in the control condition. Taken together, these results suggest that even low levels of pre-existing sleep difficulties may be buffering the impact of acute sleep deprivation on attentional biases for positive information. Participants with a history of sleep difficulties may be less sensitive to the effects of sleep loss, and therefore, may have been less affected by acute sleep deprivation. Furthermore, it is possible that acute sleep loss only impacts emotion-related attentional processes among people without a history of sleep difficulties, given

that they may have less experience being in sleep-deprived conditions, and thus have not developed coping mechanisms to modulate the effect of acute sleep loss.

4.4 Strengths and limitations

The current findings should be considered in the context of a number of study strengths and limitations. The current study used an experimental design, which allows us to infer a causal relationship between sleep deprivation and our outcome variables (i.e., cortisol and attentional biases). Furthermore, the use of random assignment allows us to systematically rule out any potential differences between groups among extraneous variables. Our analyses, however, also included a number of potentially confounding variables (e.g., age, sex, medication use, habitual sleep patterns, depressive symptomatology etc.) in our analyses. Including these covariates in our models allows us to demonstrate the robustness of the independent associations between sleep deprivation and our outcome measures. For our cortisol analyses, we used a growth curve modeling framework which addresses the limitations of more traditional approaches when examining repeated neuroendocrine data (e.g., AUC, repeated-measures ANOVA; Gueorguieva & Krystal, 2004; Hruschka et al., 2005). For example, traditional analytical approaches (i.e., AUCg) would have revealed different results, and simply reported that participants in the sleep deprivation condition had greater overall cortisol production following the stressor. Finally, saliva collections were conducted in the lab by trained staff, and thus, we were able to avoid many sampling and adherence issues commonly experienced when conducting neuroendocrine research, especially when assessing CAR (see Stalder et al., 2015 for review).

One important limitation of the current study is related to our experimental manipulation. While the current study provides support for the causal link between *total* sleep deprivation and HPA-axis functioning, it remains unclear whether variability in cortisol is simply a function of

sleep loss (and if so, what type of sleep loss) or the negative affect (e.g., irritability) associated with sleep deprivation. It is possible that sleep restriction (and not necessarily *total* sleep deprivation) or deprivation of specific stage(s) of sleep (e.g., rapid eye movement or REM sleep) may be sufficiently responsible for the effect on cortisol. Therefore, future studies that compare the differential impact of various types of sleep loss (e.g., REM sleep deprivation, sleep restriction) on subsequent HPA-axis functioning are needed. Furthermore, prospective studies may also allow us to examine the long-term consequences of acute and chronic sleep deprivation on HPA-axis stress reactivity. In addition, due to methodological limitations, we were not able to control for the effect of menstrual cycle on cortisol stress reactivity. Previous studies have demonstrated that the menstrual phase of female participants can influence cortisol responses to laboratory stressors (Kudielka & Kirschbaum, 2005). Furthermore, a high percentage of females in our sample were currently using at least one form of hormonal contraceptive, which likely blunted the overall stress response in these females. However, contraceptive use was not significantly different between the two experimental groups, and therefore, likely did not impact the first aim of the current study.

Furthermore, and specifically related to our second aim, the CAR sampling times for participants in the sleep deprivation condition occurred between 8:00 – 9:00, as they did not experience an "awakening". Consequently, it is possible that we missed many participants' CAR, or their "window" for CAR, given the individual variability in chronotype and habitual waketime. Yet, we used an experimental design and random assignment to systematically rule out any potential differences between groups among these variables. In addition, we assessed habitual sleep patterns via actigraphy during the week prior to coming into the lab, and were therefore, able to control for any variability accounted for by habitual sleep/wake time. Furthermore,

previous studies have demonstrated that among young adults under constant conditions (i.e., sleep-deprived, 24-hour monitoring), the acrophase in plasma cortisol occurs approximately between 08:00 – 09:00 (Monk et al., 1997; Van Cauter, Leproult, & Kupfer, 1996). We also controlled for differences in morningness-eveningness (via the MEQ), and while the main effect of MEQ was significant, this effect was relatively smaller and independent of the group effect. Future studies, however, should use alternative cortisol collection methods that are more sensitive to the continuous fluctuations in cortisol and able to assess cortisol throughout the night and morning (e.g., urinary free cortisol, plasma cortisol). It is also possible that our findings may be due to a lack of exposure to light change among participants in the sleep deprivation condition. The current study was conducted indoors and so the sleep-deprived participants did not experience the lights-out to lights-on transition. Studies suggest that light exposure is associated with changes in cortisol (Foret, Aguirre, Touitou, Clodore, & Benoit, 1993), and thus, follow-up studies should also consider this as an alternative explanation. However, light levels remained constant and at approximately 0 – 40 lux for participants in the sleep deprivation condition.

Another important limitation, specifically related to our third and final aim, is that the range of self-reported sleep difficulties or insomnia symptoms was relatively low (range = 0 – 13), and suggests that our sample was composed of generally good sleepers. Therefore, any findings related to the independent or interactive role of self-reported sleep difficulties should be interpreted with caution. These findings may not necessarily be generalizable to individuals with 'true' insomnia symptoms or genuine sleep difficulties. Certainly, the current sample was not representative of a clinical population, and therefore, it is essential for follow-up studies to examine the direct impact of sleep deprivation on attentional biases to positive information among participants with clinically elevated insomnia symptoms or insomnia disorder. However,

this is the first study to examine sleep [loss] under controlled conditions, and therefore, it does shed some light on the potential role of sleep deprivation in creating attentional biases for or away from emotionally-valenced information.

Finally, this study represents data from a relatively small sample, which is predominantly composed of highly educated young adults (75% of sample included undergraduate and graduate students). Therefore, the results of this study may not be generalizable to other age groups or "non-healthy" populations. Despite this, the sample's age range was relatively large (range = 18 − 29) and not a traditional "college sample". Nonetheless, subsequent studies should examine factors that impact CAR among more heterogeneous samples, including clinical populations.

4.5 Conclusions

In conclusion, the current study advances our understanding of the direct link between experimental sleep loss and HPA-axis stress reactivity. Specifically, this was the first study to use a carefully controlled sleep manipulation to examine whether sleep deprivation had a direct impact on cortisol reactivity to a widely used laboratory stress task (i.e., TSST). Our findings provided further support for the notion that sleep deprivation has an effect on cortisol under non-stressful conditions (i.e., elevated baseline cortisol). Yet, sleep deprivation has the opposite effect on cortisol reactivity to stress, at least in a healthy sample of young adults, such that sleep deprivation was associated with a reduced or blunted cortisol stress response. The current study also advances our limited understanding of CAR's biopsychosocial meaning. Using a carefully controlled experimental design, we examined whether CAR was influenced by the HPA-axis' circadian drive independently of the awakening process, or instead, a response that was fully dependent on awakening. Specifically, our findings support that CAR is dependent on the transition from sleep to awakening, and not simply a part of cortisol's general circadian rhythm.

In addition, the current study also highlights the importance of considering the impact third variables (e.g., biological sex, affect, chronotype) may have in determining the timing and intensity of cortisol responses to stress and awakening (i.e., CAR). Finally, the current study was the first to examine the direct link between experimental sleep loss and attentional biases to emotional information. Specifically, our findings showed that sleep deprivation had a negative relationship with attentional biases to positive stimuli, but that this link was modulated by participants' current history of self-reported sleep difficulties. These findings have important implications for understanding the cognitive processes that are involved in the development and maintenance of stress-related disorders, in particular, insomnia.

Tables

Table 1. Correlations (Pearson's *r*) between all continuous demographic variables and other covariates.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
(1) Age	--																
(2) ISI	0.17	--															
(3) PSQI	0.29	.72**	--														
(4) MEQ	.41**	-0.21	-0.15	--													
(5) Epworth	0.05	0.23	.45**	0.04	--												
(6) TIB	-0.05	-.42**	-0.27	0.10	-0.07	--											
(7) TST	-0.05	-.40*	-0.25	0.02	-0.08	.94**	--										
(8) %SE	0.02	-0.04	0.00	-0.19	-0.11	0.10	.43**	--									
(9) SOL	-0.05	0.02	0.15	-0.29	-0.02	0.20	0.20	0.06	--								
(10) WASO	0.00	-0.07	-0.06	0.23	0.04	0.21	-0.14	-.94**	0.00	--							
(11) Awakenings	0.02	-0.16	-0.23	.33*	-0.11	0.31	0.01	-.76**	0.05	.87**	--						
(12) PHQ9	0.29	.72**	.51**	-0.12	0.17	-0.24	-0.26	-0.09	0.07	0.04	0.01	--					
(13) GAD7	0.22	.41**	0.31	-0.29	-0.01	-0.19	-0.14	0.07	0.30	-0.13	-0.20	.56**	--				
(14) PANAS (Neg)	-0.15	0.13	-0.05	0.10	-0.11	-0.15	-0.18	-0.15	-0.13	0.10	0.07	0.18	0.17	--			
(15) PANAS (Pos)	0.10	-0.08	-0.07	0.18	-0.29	0.24	0.12	-0.30	0.31	.38*	.43**	-0.23	-0.04	-0.02	--		
(16) PSS	0.12	.35*	0.25	-0.12	0.05	-0.23	-0.17	0.14	-0.02	-0.19	-0.30	.40*	.52**	.37*	-0.25	--	
(17) PERI-LES	-0.04	-0.09	-0.04	-0.04	0.03	0.22	0.22	0.05	.75**	0.01	0.13	0.10	0.26	-0.05	.37*	-0.18	--

* p < .05; ** p < .01;

Table 2. Means, standard deviations, and *p*-values for all demographic, sleep, mood, stress, and attentional bias variables for both experimental conditions (sleep deprivation versus control).

	Control Group (*n* = 20)	Sleep Deprived Group (*n* = 20)	*p*-value
Age, mean (SD)	23.1 (3.25)	22.3 (3.05)	0.46
ISI, mean (SD)	4.05 (3.61)	5.05 (3.79)	0.40
PSQI, mean (SD)	4.45 (2.56)	4.60 (2.28)	0.85
MEQ, mean (SD)	45.0 (6.68)	47.3 (8.00)	0.33
ESS, mean (SD)	6.15 (3.42)	6.20 (4.84)	0.97
Actigraphy Data, mean (SD)			
TIB, *in min*	462.82 (38.9)	428.28 (40.8)	0.01
TST, *in min*	419.8 (39.0)	388.4 (40.9)	0.02
%SE, *in min*	90.7 (2.96)	90.6 (3.52)	0.94
SOL, *in min*	14.2 (17.4)	8.5 (6.01)	0.19
WASO, *in min*	43.1 (14.3)	39.8 (15.2)	0.51
Awakenings	23.8 (7.8)	22.0 (7.8)	0.48
PHQ-9, mean (SD)	1.6 (1.64)	2.2 (1.61)	0.25
GAD-7, mean (SD)	2.0 (1.89)	1.9 (1.89)	0.87
PANAS-N, mean (SD)	10.6 (1.00)	12.6 (2.59)	0.002
PANAS-P, mean (SD)	15.6 (5.53)	12.2 (3.21)	0.03
PSS, mean (SD)	9.3 (4.55)	13.3 (5.70)	0.02
PERI-LES, mean (SD)	32.8 (103.2)	8.0 (10.8)	0.29
Negative Bias	-2.82 (28.4)	-12.68 (22.3)	0.23
Positive Bias	2.69 (17.5)	-2.00 (25.5)	0.50

Table 3. Means, standard deviations, and *p*-values for morning cortisol and cortisol in response to the Trier Social Stress Test (TSST).

	Control Group (*n* = 20)	Sleep Deprived Group (*n* = 20)	*p*-value
CAR, *ug/dl*, mean (SD)			
+0 min post-awakening	0.24 (0.13)	0.27 (0.14)	0.52
+30 min post-awakening	0.40 (0.17)	0.30 (0.15)	0.04
+45 min post-awakening	0.39 (017)	0.25 (0.13)	0.01
+60 min post-awakening	0.37 (0.17)	0.25 (0.17)	0.03
+120 min post-awakening	0.23 (0.14)	0.25 (0.14)	0.62
+150 min post-awakening	0.22 (0.15)	0.27 (0.19)	0.32
TSST *ug/dl*, mean (SD)			
-10 min post-TSST	0.14 (0.07)	0.21 (0.11)	0.04
0 min post-TSST	0.14 (0.12)	0.18 (0.17)	0.14
+10 min post-TSST	0.18 (0.14)	0.25 (0.16)	0.15
+15 min post-TSST	0.26 (0.14)	0.38 (0.29)	0.12
+20 min post-TSST	0.34 (0.18)	0.47 (0.37)	0.20
+25 min post-TSST	0.37 (0.23)	0.50 (0.39)	0.22
+30 min post-TSST	0.41 (0.26)	0.48 (0.34)	0.41
+35 min post-TSST	0.35 (0.23)	0.41 (0.29)	0.49
+40 min post-TSST	0.32 (0.18)	0.38 (0.25)	0.39
+50 min post-TSST	0.28 (0.16)	0.35 (0.18)	0.24
+60 min post-TSST	0.24 (0.13)	0.29 (0.14)	0.25

Table 4. Regression estimates from our final adjusted model with the main effects of condition, sex, positive affect, and negative affect predicting cortisol reactivity in response to the TSST. *b* values and SE were multiplied by a constant (i.e., 100) to ease interpretation.

	Awakening Cortisol			Linear Slope			Quadratic Slope		
	b	SE	*t*-value	*b*	SE	*t*-value	*b*	SE	*t*-value
Model 1									
Group	-69.50	32.33	-2.15*	2.394	0.960	2.49*	-0.027	-0.011	-2.36*
Sex	21.93	32.81	0.67	3.198	0.974	3.28**	-0.037	0.011	-3.23**
Caffeine Use	-63.26	39.35	-1.61	3.753	1.168	3.21**	-0.048	0.014	-3.52***
Model 2									
Group	-73.05	44.77	-1.63	0.303	1.286	2.35*	-0.041	0.015	-2.69**
Positive Affect	0.848	149.7	0.01	9.518	4.300	2.21*	-0.121	0.050	-2.40*
Negative Affect	-58.07	299.1	-0.19	21.22	8.585	2.47*	-0.317	0.100	-3.15**

* p < .05; ** p < .01; *** p < .001

Table 5. Regression estimates from our unadjusted covariate models with the main effects of demographic, sleep, mood, and stress variables predicting the cortisol awakening response (CAR). *b* values and SE were multiplied by a constant (i.e., 100) to ease interpretation.

	Awakening Cortisol			Linear Slope			Quadratic Slope		
	b	SE	*t*-value	*b*	SE	*t*-value	*b*	SE	*t*-value
Sex	-1.886	7.098	-0.27	-0.1227	0.1613	-0.76	0.0005	0.0009	0.59
Age	-0.822	1.143	-0.72	-0.0250	0.0258	-0.97	<0.0001	0.0002	-0.06
Birth Control	7.506	10.906	0.69	-0.2132	0.2418	-0.88	0.0016	0.0014	1.15
GAD	-1.243	1.927	-0.65	0.0263	0.0437	0.60	-0.0002	0.0003	-0.62
PHQ9	-0.875	2.205	-0.40	-0.0121	0.0501	-0.24	0.0001	0.0003	0.29
PSS	-0.764	0.633	-1.21	-0.0087	0.0148	-0.59	0.0001	0.0001	1.16
ISI	-1.084	0.966	-1.12	0.0092	0.0221	0.42	<0.0001	0.0001	-0.32
PERI-LES	0.012	0.051	0.23	0.0005	0.0011	0.44	<0.0001	0.0000	-0.04
Epworth	-1.491	0.858	-1.74	0.0314	0.0196	1.60	-0.0002	0.0001	-1.93
PSQI	-1.535	1.492	-1.03	0.0191	0.0340	0.56	-0.0001	0.0002	-0.55
MEQ	0.228	0.488	0.47	-0.0286	0.0109	-2.62**	0.0001	0.0001	2.06*
TST	-0.006	0.084	-0.08	-0.0001	0.0020	-0.03	<0.0001	0.0000	0.40
%SE	0.403	1.110	0.36	-0.0023	0.0264	-0.09	0.0001	0.0002	0.54
SOL	-0.040	0.275	-0.15	0.0009	0.0065	0.14	<0.0001	0.0000	0.34
WASO	-0.053	0.244	-0.22	-0.0016	0.0058	-0.28	<0.0001	0.0000	-0.09
Awakenings	0.252	0.461	0.55	-0.0141	0.0108	-1.31	0.0001	0.0001	1.05
PANAS (POS)	0.415	0.729	0.57	0.0083	0.0173	0.48	-0.0001	0.0001	-1.04
PANAS (NEG)	0.132	1.640	0.08	-0.0525	0.0386	-1.36	0.0003	0.0002	1.43

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 6. Regression estimates from our final adjusted model with the main effects of condition and morningness-eveningness scores (MEQ) predicting the cortisol awakening response (CAR). *b* values and SE were multiplied by a constant (i.e., 100) to ease interpretation.

	Awakening Cortisol			Linear Slope			Quadratic Slope		
	β	SE	*t*-value	β	SE	*t*-value	β	SE	*t*-value
Unadjusted Model									
Group Effect	0.614	6.681	0.09	-0.5942	0.1507	-3.94***	0.0045	0.0009	5.23***
Adjusted Model									
Group Effect	0.102	6.832	0.02	-0.5422	0.1508	-3.59***	-0.0043	0.0009	-4.97***
MEQ	0.231	0.470	0.49	-0.0230	0.0104	-2.22*	0.0001	0.0001	1.46
* p < .05; ** p < .01; *** p < .001									

Table 7. Regression estimates from our unadjusted covariate models with the main effects of sleep, mood, and stress variables predicting attentional biases to negative and positive stimuli.

	Negative Bias			Positive Bias		
	b	SE	*t*	*b*	SE	*t*
PHQ-9	3.25	2.13	1.53	-0.07	1.74	-0.04
PSS	0.04	0.66	0.06	0.08	0.51	0.16
PSQI	0.20	1.53	0.13	0.21	1.25	0.17
TST	0.15	0.10	1.54	-0.01	0.07	-0.11
NA	1.77	1.69	1.04	0.96	1.30	0.74
PA	-0.50	0.77	-0.66	0.60	0.58	1.03

* $p < .05$, ** $p < .01$

Table 8. Regression estimates from our final adjusted models with the main effects and interaction effects of condition and self-reported sleep difficulties (ISI) predicting biases to negative and positive stimuli.

	b	SE	t	p-value
Negative Bias				
ISI	-1.56	7.28	-0.21	0.83
Group	-3.42	7.28	-0.47	0.64
ISI X Group	14.93	14.55	1.03	0.31
Positive Bias				
ISI	10.22	5.26	1.94	0.06
Group	-8.56	5.26	-1.63	0.11
ISI X Group	-15.66	10.34	-1.52	0.14

Figures

Figure 1. Prototypical cortisol awakening response (CAR) and diurnal cortisol rhythm over a 24-hour period in a 'healthy' participant.
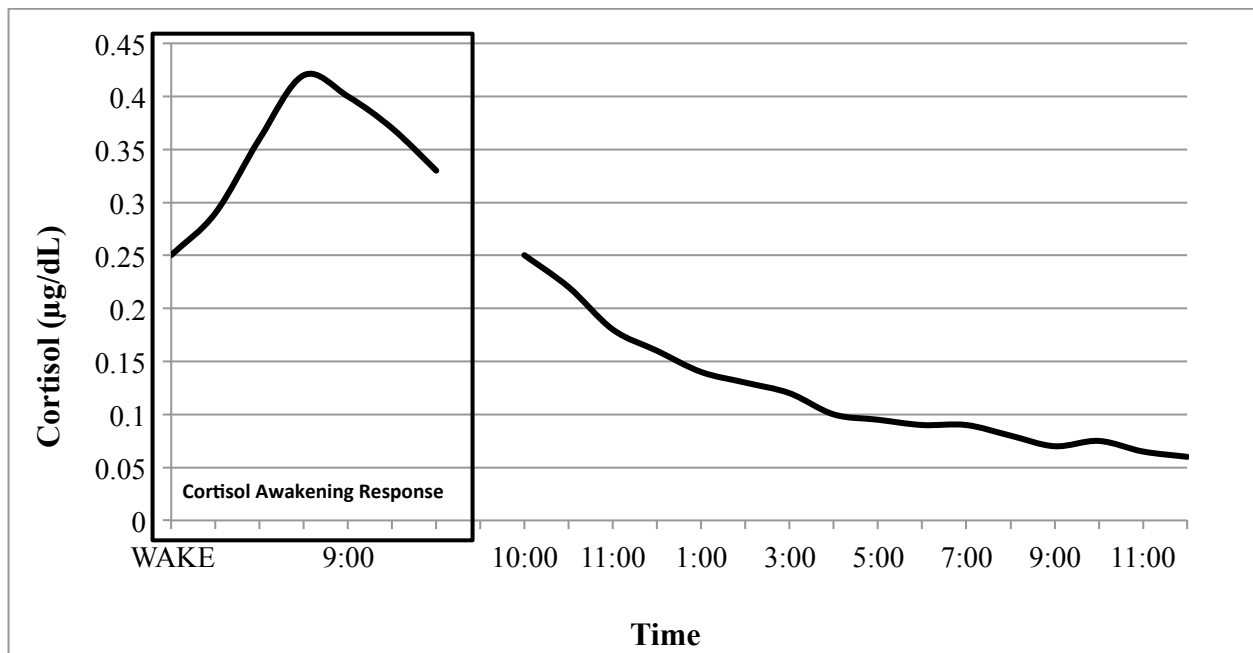
Figure 2. Estimated morning cortisol from awakening as a function of total sleep time among a sample of healthy college students (reprinted from Vargas & Lopez-Duran, 2014, *Psychoneuroendocrinology*).
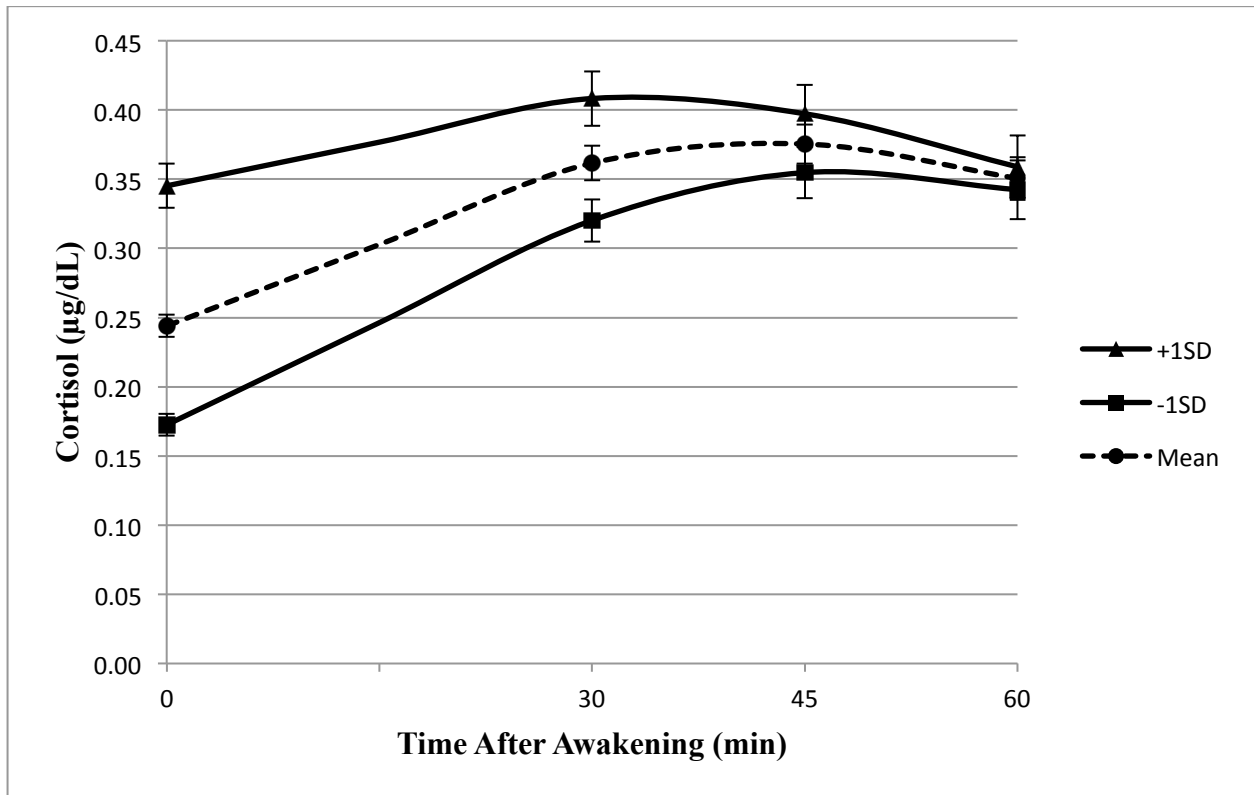
Figure 3. Study timeline and activity flowchart.
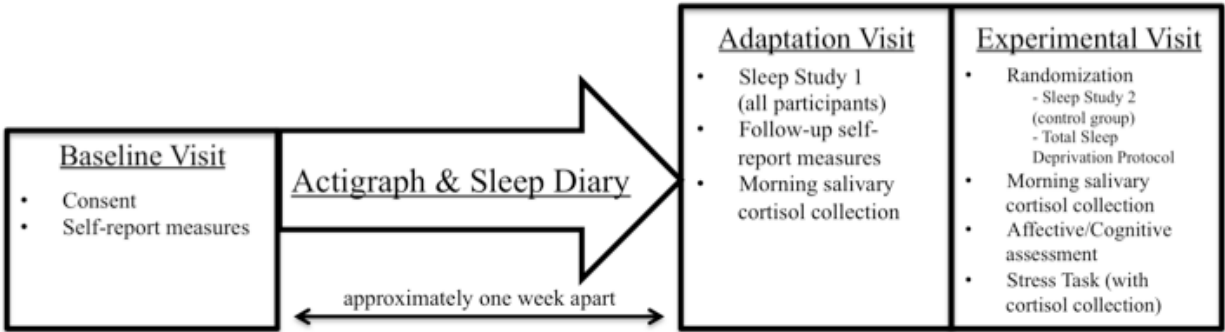
Figure 4. Experimental day timeline and saliva sampling.
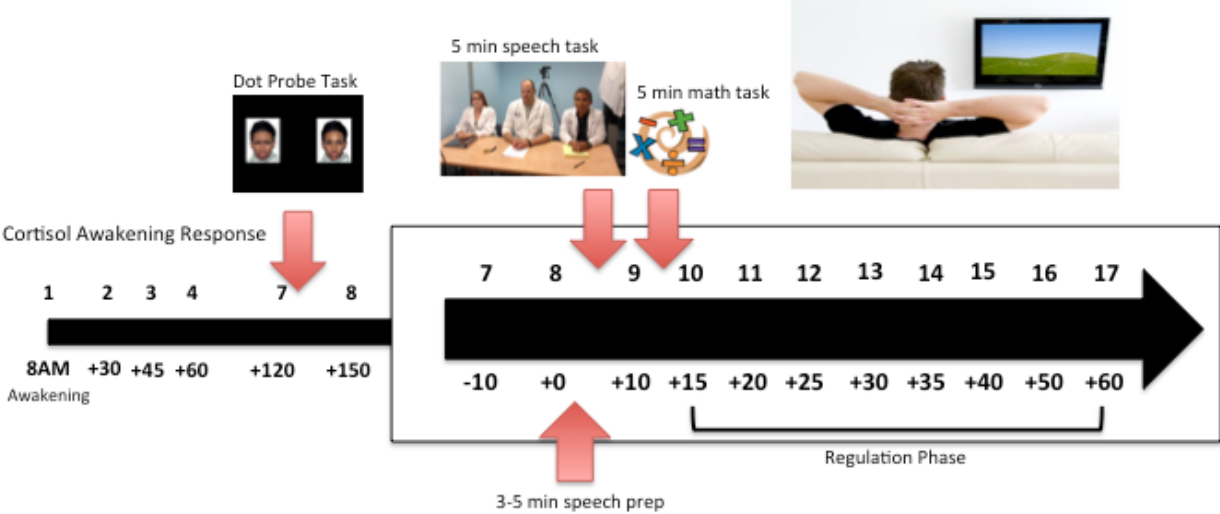
Figure 5. Graphic representation of modified Dot Probe Task. Following a brief (1500 ms) presentation of two images, participants were asked to indicate whether the dot probe is on the right or left-hand-side of the screen.
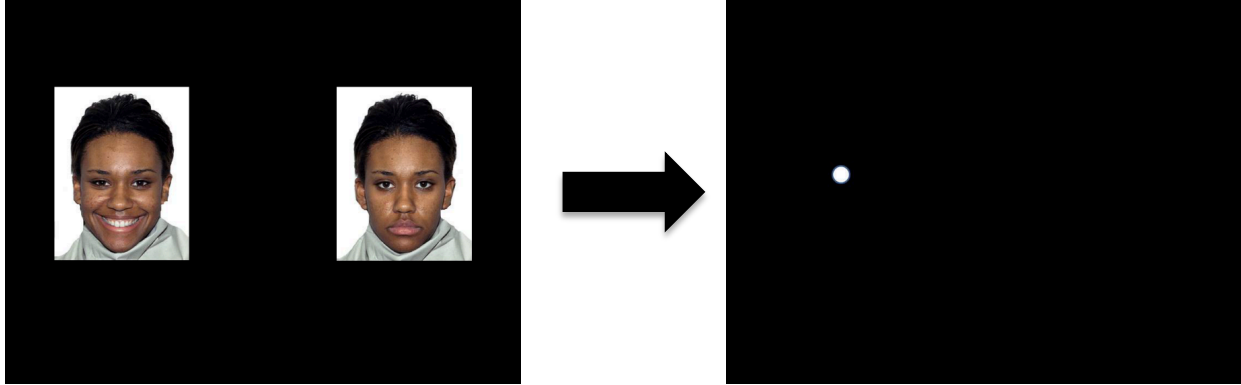
Figure 6. Mean cortisol awakening response (CAR) and standard errors for both experimental conditions.
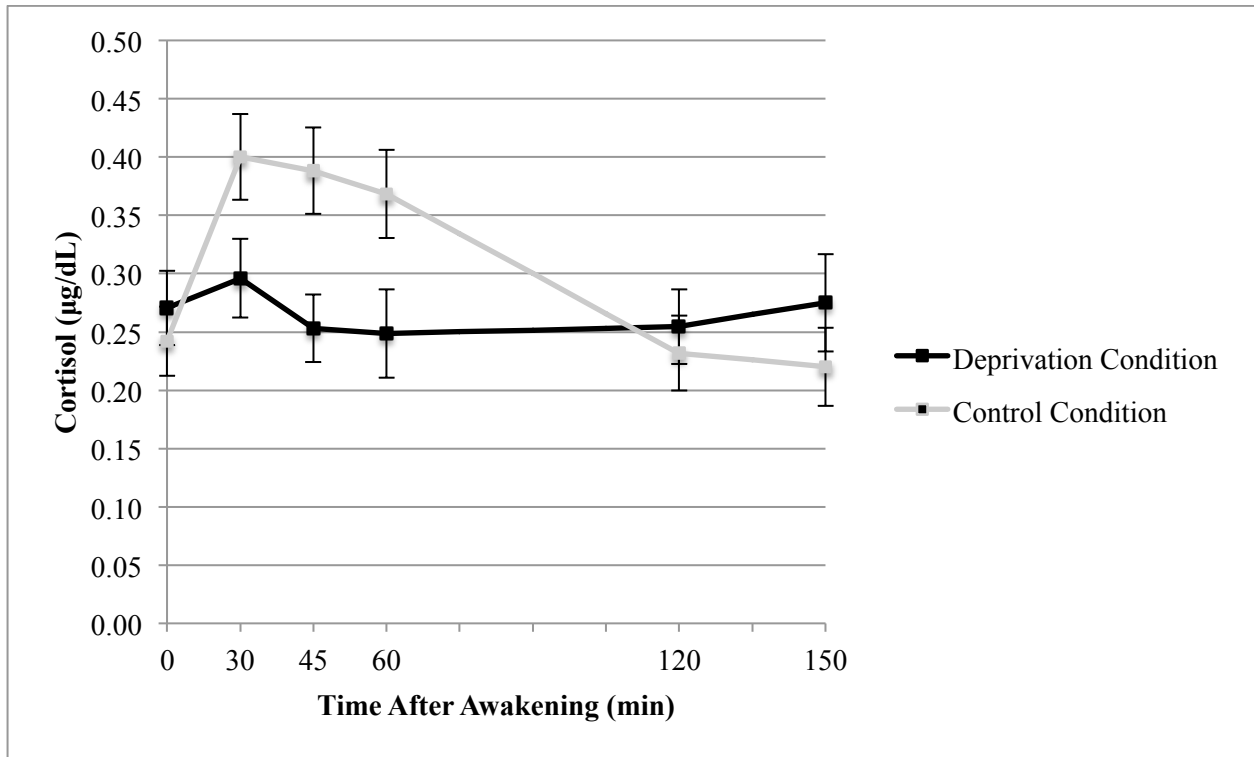
Figure 7. Mean cortisol reactivity and standard errors in response to the Trier Social Stress Test (TSST) for both experimental conditions.
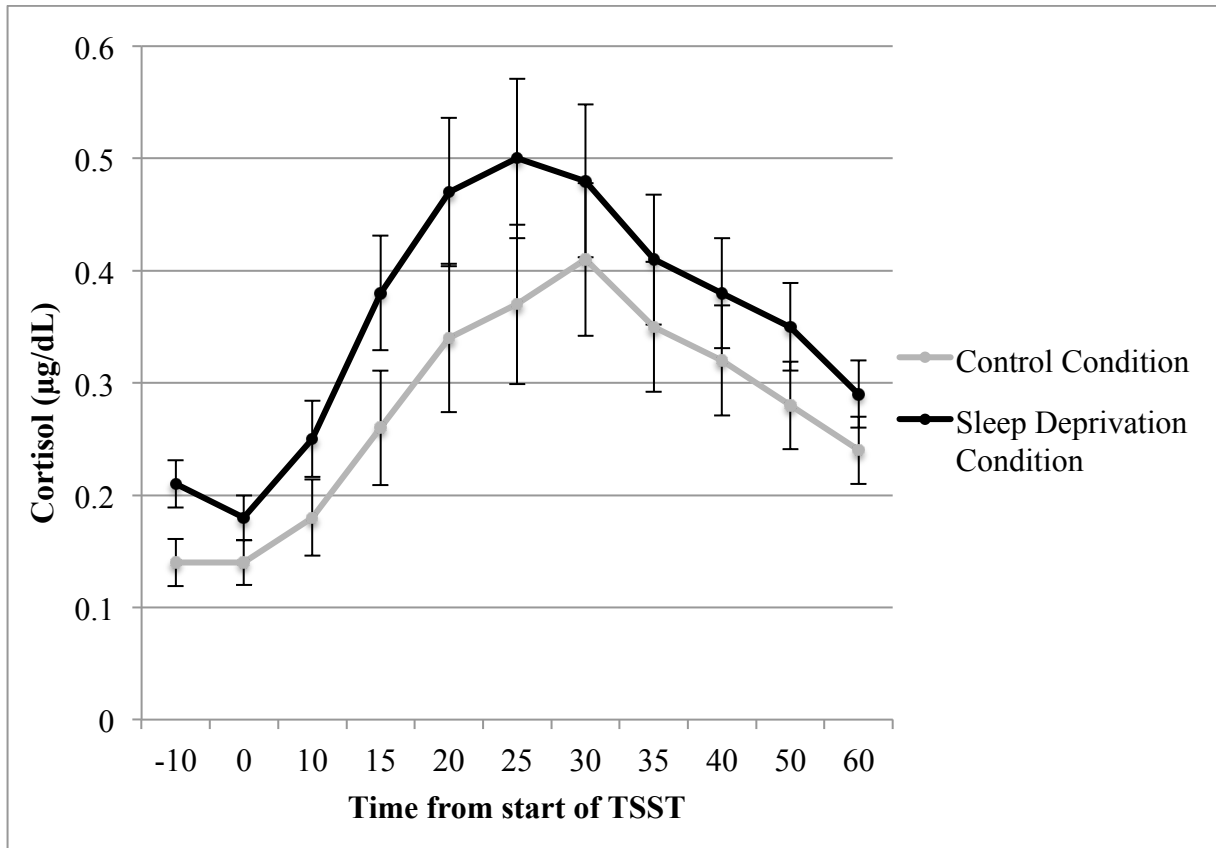
Figure 8. Estimated, unadjusted effect of experimental condition on cortisol response to the TSST.
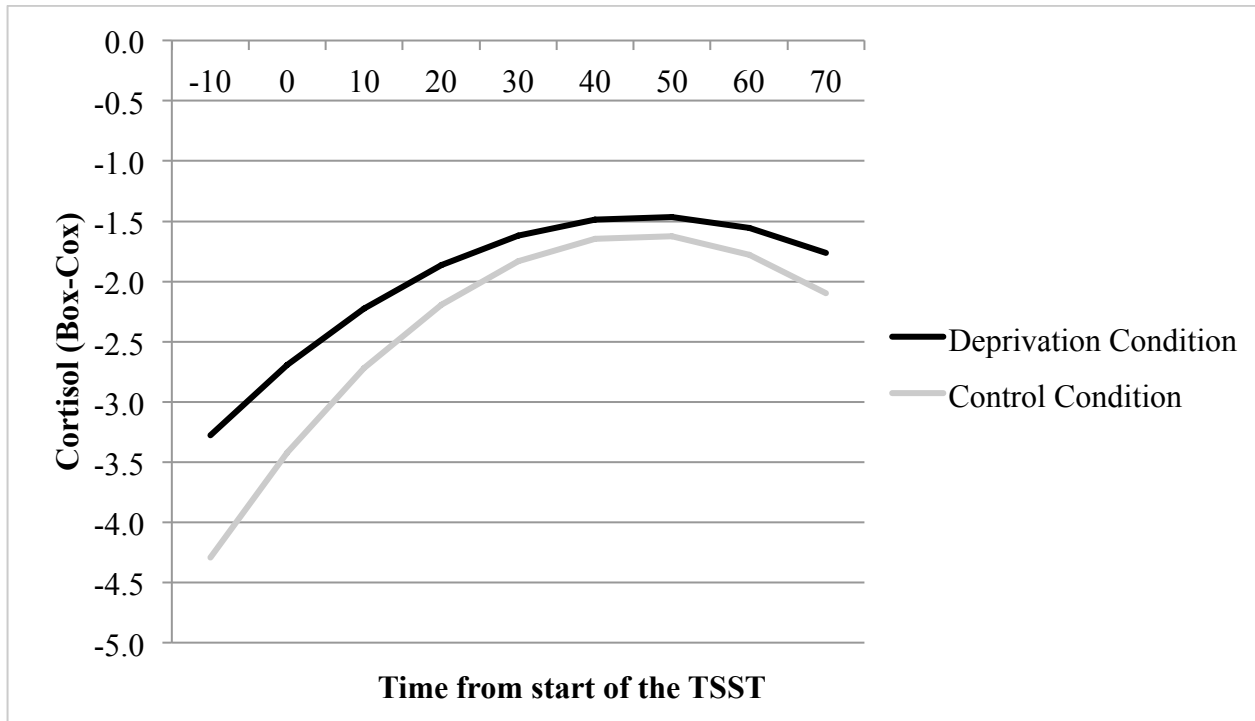
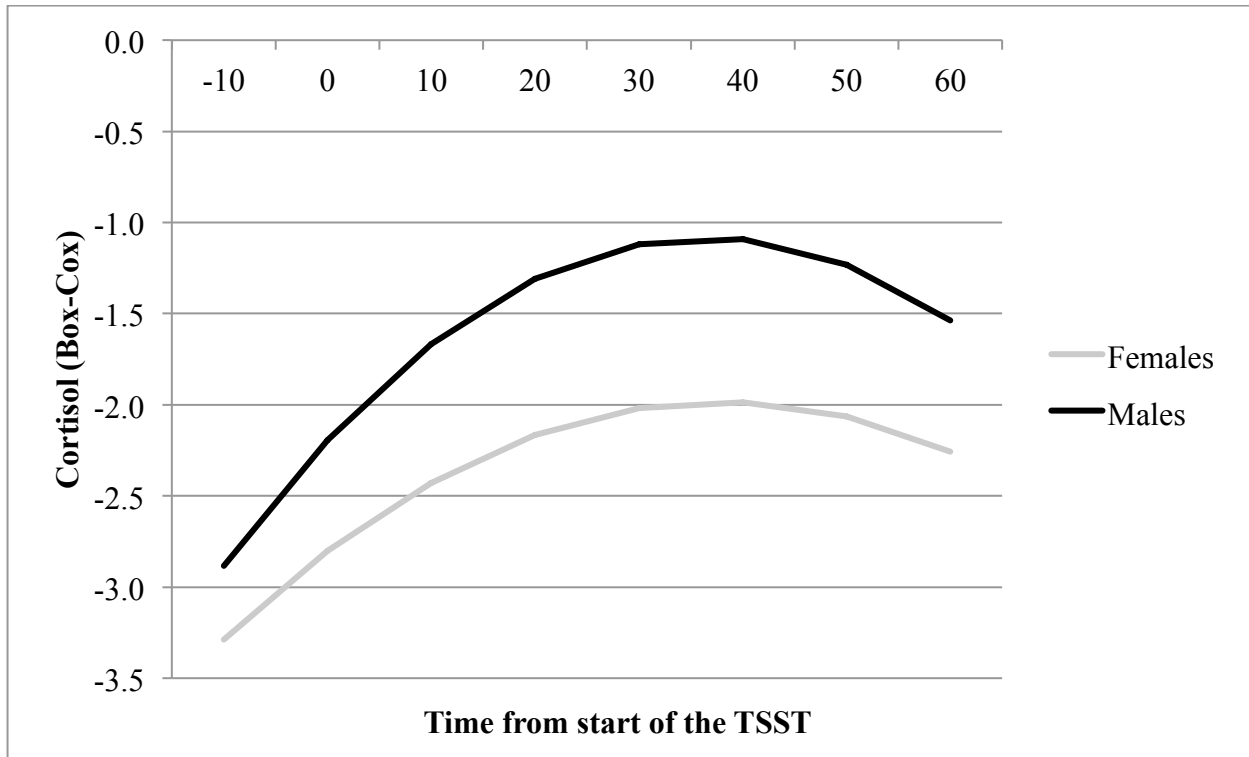Figure 9. Estimated, adjusted effect of biological sex on cortisol response to the TSST.
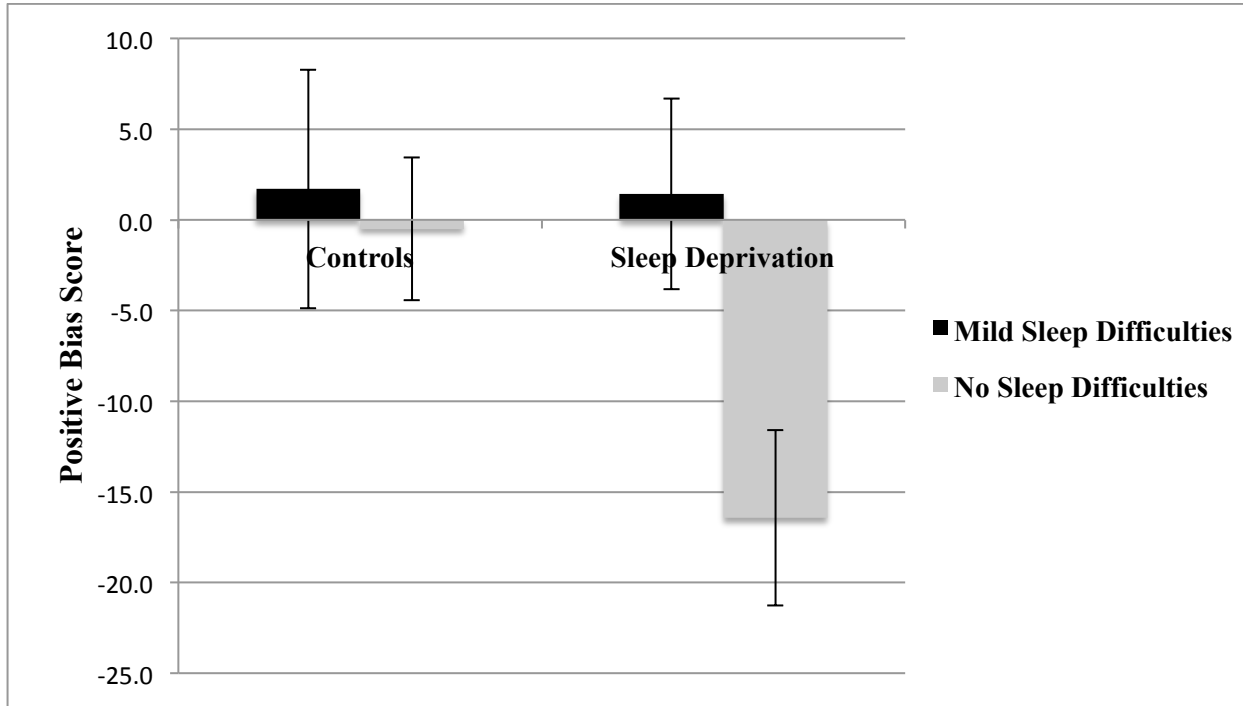
Figure 10. Estimated, adjusted effect of condition and sleep difficulties (ISI scores) on attentional biases to positive stimuli.

References

Abelson, J. L., Khan, S., Liberzon, I., Erickson, T. M., & Young, E. A. (2008). Effects of Perceived Control and Cognitive Coping on Endocrine Stress Responses to Pharmacological Activation. *Biological Psychiatry*, *64*(8), 701–707. doi:10.1016/j.biopsych.2008.05.007

Adan, A., Archer, S., & Hidalgo, M. (2012). Circadian typology: A comprehensive review. *Chronobiology International: The Journal of Biological and Medical Rhythm Research*, *29*(9), 1153–1175. Retrieved from http://www.tandfonline.com/doi/abs/10.3109/07420528.2012.719971

Al'Absi, M., Lovallo, W. R., McKey, B., Sung, B. H., Whitsett, T. L., & Wilson, M. F. (1998). Hypothalamic-pituitary-adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. *Psychosomatic Medicine*, *60*, 521–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9710300

Altena, E., Van Der Werf, Y. D., Strijers, R. L. M., & Van Someren, E. J. W. (2008). Sleep loss affects vigilance: effects of chronic insomnia and sleep therapy. *Journal of Sleep Research*, *17*(3), 335–43. doi:10.1111/j.1365-2869.2008.00671.x

Balbo, M., Leproult, R., & Van Cauter, E. (2010). Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity. *International Journal of Endocrinology*, *1*, 1–16. doi:10.1155/2010/759234

Balkin, T., Braun, A., & Wesensten, N. (2002). The process of awakening: a PET study of

regional brain activity patterns mediating the re-establishment of alertness and

consciousness. *Brain*, *125*, 2308–2319. Retrieved from

http://brain.oxfordjournals.org/content/125/10/2308.short

Bar-Haim, Y., Lamy, D., Lee, P., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H.

(2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-

analytic study. *Psychological Bulletin*, *133*(1), 1–24. Retrieved from

http://psycnet.apa.org/?fa=main.doiLanding&doi=10.1037/0033-2909.133.1.1

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index

as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307.

doi:10.1016/S1389-9457(00)00065-4

Beevers, C. G., & Carver, C. S. (2003). Attentional bias and mood persistence as prospective

predictors of dysphoria. *Cognitive Therapy and Research*, *27*(6), 619–637.

doi:10.1023/A:1026347610928

Born, J., & Fehm, H. (1997). Hypothalamus-pituitary-adrenal activity during human sleep: a

coordinating role for the limbic hippocampal system. *Experimental and Clinical

Endocrinology & Diabetes*, *106*(3), 153–163. Retrieved from

http://europepmc.org/abstract/med/9710353

Born, J., Hansen, K., Marshall, L., Mölle, M., & Fehm, H. L. (1999). Timing the end of

nocturnal sleep. *Nature*, *397*(6714), 29–30. doi:10.1038/16166

Born, J., Kern, W., Bieber, K., Fehm-Wolfsdorf, G., Schiebe, M., & Fehm, H. (1986). Night-

time plasma cortisol secretion is associated with specific sleep stages. *Biological Psychiatry*, *21*(1), 1415–1424. Retrieved from

http://www.sciencedirect.com/science/article/pii/0006322386903331

Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996). Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biological Psychiatry*, *39*(6), 411–418. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8679786

Buckley, T. M., & Schatzberg, A. F. (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *The Journal of Clinical Endocrinology and Metabolism*, *90*(5), 3106–14. doi:10.1210/jc.2004-1056

Burke, H., Davis, M., Otte, C., & Mohr, D. (2005). Depression and cortisol responses to psychological stress: a meta-analysis. *Psychoneuroendocrinology*, *30*, 846–856. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453005000831

Buysse, D. J., Angst, J., Gamma, A., Ajdacic, V., Eich, D., & Rössler, W. (2008). Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep*, *31*(4), 473–80. doi:10.5167/uzh-10110

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2748771

Capaldi, V., Handweger, K., Richardson, E., & Stroud, L. (2005). Associations between sleep

and cortisol responses to stress in children and adolescents: A pilot study. *Behavioral Sleep Medicine*, *3*(4), 177–192.

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep*, *35*(2), 287–302. doi:10.5665/sleep.1642

Carpenter, J. S., & Andrykowski, M. a. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of Psychosomatic Research*, *45*(1), 5–13. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9720850

Chida, Y., & Steptoe, A. (2009). Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. *Biological Psychology*, *80*(3), 265–278. Retrieved from http://www.sciencedirect.com/science/article/pii/S0301051108002202

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*, *30*(2), 203–16. doi:10.1016/j.cpr.2009.11.003

Clow, A., Hucklebridge, F., Stalder, T., Evans, P., & Thorn, L. (2010). The cortisol awakening response: more than a measure of HPA axis function. *Neuroscience and Biobehavioral Reviews*, *35*(1), 97–103. doi:10.1016/j.neubiorev.2009.12.011

Clow, A., Hucklebridge, F., & Thorn, L. (2010). *The cortisol awakening response in context. International review of neurobiology* (Vol. 93). Elsevier Inc. doi:10.1016/S0074-7742(10)93007-9

Clow, A., Thorn, L., Evans, P., & Hucklebridge, F. (2004). The awakening cortisol response:

methodological issues and significance. *Stress*, *7*(1), 29–37. Retrieved from

http://www.tandfonline.com/doi/abs/10.1080/10253890410001667205

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress.

Journal of Health and Social Behavior, *24*(4), 385–396. Retrieved from

http://www.jstor.org/stable/2136404

Czeisler, C., Duffy, J., & Shanahan, T. (1999). Stability, precision, and near-24-hour period of

the human circadian pacemaker. *Science*, *284*, 2177–2181. Retrieved from

http://www.sciencemag.org/content/284/5423/2177.short

de Kloet, E. R. (1991). Brain Corticosteroid Receptor Balance and Homeostatic Control.

Frontiers in Neuroendocrinology, *12*(2), 95–164. doi:10.1080/09614520701469617

Devine, J. K., & Wolf, J. M. (2016). Determinants of cortisol awakening responses to naps and

nighttime sleep. *Psychoneuroendocrinology*, *63*, 128–134.

doi:10.1016/j.psyneuen.2015.09.016

Dinges, D., Douglas, S., Hamarman, S., Zaugg, L., & Kapoor, S. (1995). Sleep deprivation and

human immune function. *Advances in Neuroimmunology*, *5*(2), 97–110. Retrieved from

http://www.sciencedirect.com/science/article/pii/096054289500002J

Dohrenwend, B., Krassnoff, L., & Askenasy, A. (1978). Exemplification of a method for scaling

life events: The PERI Life Events Scale. *Journal of Health and Social Behavior*, *19*(2),

205–229. Retrieved from http://www.jstor.org/stable/2136536

Doi, Y., Minowa, M., Uchiyama, M., Okawa, M., Kim, K., Shibui, K., & Kamei, Y. (2000).

Psychometric assessment of subjective sleep quality using the Japanese version of the

Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Research*, *97*(2-3), 165–172. doi:10.1016/S0165-1781(00)00232-8

Drake, C., Roehrs, T., Burduvali, E., Bonahoom, A., Rosekind, M., & Roth, T. (2001). Effects of rapid versus slow accumulation of eight hours of sleep loss. *Psychophysiology*, *38*(6), 979–987. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/1469-8986.3860979/full

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive Consequences of Sleep Deprivation. *Seminars in Neurology*, *25*(1), 117–129.

Edwards, S., Evans, P., Hucklebridge, F., & Clow, A. (2001). Association between time of awakening and diurnal cortisol secretory activity. *Psychoneuroendocrinology*, *26*(6), 613–22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11403981

Ekstedt, M., Åkerstedt, T., & Söderström, M. (2004). Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. *Psychosomatic Medicine*, *66*(6), 925–931. doi:10.1097/01.psy.0000145821.25453.f7

El-Sheikh, M., Buckhalt, J. a, Keller, P. S., & Granger, D. a. (2008). Children's objective and subjective sleep disruptions: links with afternoon cortisol levels. *Health Psychology*, *27*(1), 26–33. doi:10.1037/0278-6133.27.1.26

Elder, G. J., Wetherell, M. a, Barclay, N. L., & Ellis, J. G. (2013). The cortisol awakening response--applications and implications for sleep medicine. *Sleep Medicine Reviews*, *18*(3), 215–224. doi:10.1016/j.smrv.2013.05.001

Espie, C. A. (2002). Insomnia: conceptual issues in the development, persistence, and treatment of sleep disorder in adults. *Annual Review of Psychology*, *53*, 215–43.

doi:10.1146/annurev.psych.53.100901.135243

Espie, C. A., Broomfield, N. M., MacMahon, K. M. A., Macphee, L. M., & Taylor, L. M. (2006).
The attention-intention-effort pathway in the development of psychophysiologic insomnia:
a theoretical review. *Sleep Medicine Reviews*, *10*(4), 215–45.
doi:10.1016/j.smrv.2006.03.002

Federenko, I., Wüst, S., Hellhammer, D. H., Dechoux, R., Kumsta, R., & Kirschbaum, C. (2004).
Free cortisol awakening responses are influenced by awakening time.
Psychoneuroendocrinology, *29*(2), 174–184. doi:10.1016/S0306-4530(03)00021-0

Foret, J., Aguirre, A., Touitou, Y., Clodore, M., & Benoit, O. (1993). Effect of morning bright
light on body temperature, plasma cortisol and wrist motility measured during 24 hour of
constant conditions. *Neuroscience Letters*, *155*, 155–158. Retrieved from
http://www.sciencedirect.com/science/article/pii/030439409390696I

Fortier-Brochu, E., Beaulieu-Bonneau, S., Ivers, H., & Morin, C. M. (2012). Insomnia and
daytime cognitive performance: a meta-analysis. *Sleep Medicine Reviews*, *16*(1), 83–94.
doi:10.1016/j.smrv.2011.03.008

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR):
facts and future directions. *International Journal of Psychophysiology*, *72*(1), 67–73.
doi:10.1016/j.ijpsycho.2008.03.014

Gallicchio, L., & Kalesan, B. (2009). Sleep duration and mortality: a systematic review and
meta-analysis. *Journal of Sleep Research*, *18*(2), 148–158. Retrieved from
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2869.2008.00732.x/full

Gangwisch, J., Heymsfield, S., Boden-Albala, B., Buijs, R. M., Kreier, F., Pickering, T. G., & Malaspina, D. (2006). Short sleep duration as a risk factor for hypertension analyses of the first national health and nutrition examination survey. *Hypertension*, *47*(5), 833–839. Retrieved from http://hyper.ahajournals.org/content/47/5/833.short

Goodin, B. R., Smith, M. T., Quinn, N. B., King, C. D., & McGuire, L. (2012). Poor sleep quality and exaggerated salivary cortisol reactivity to the cold pressor task predict greater acute pain severity in a non-clinical sample. *Biological Psychology*, *91*(1), 36–41. doi:10.1016/j.biopsycho.2012.02.020

Gotlib, I. H., Krasnoperova, E., Neubauer Yue, D., & Joormann, J. (2004). Attentional Biases for Negative Interpersonal Stimuli in Clinical Depression. *Journal of Abnormal Psychology*, *113*(1), 127–135. doi:10.1037/0021-843X.113.1.127

Gotlib, I., & Neubauer, D. (2000). Information-processing approaches to the study of cognitive biases in depression. In S. Johnson, A. Hayes, Ti. Field, N. Schneiderman, & P. McCabe (Eds.), *Stress, Coping, and Depression* (pp. 117–142). Mahwah, New Jersey: Lawrence Erlbaum Associates, Inc. Retrieved from https://books.google.com/books?hl=en&lr=&id=o4x5AgAAQBAJ&oi=fnd&pg=PA117&dq=Information-processing+approaches+to+the+study+of+cognitive+biases+in+depressio&ots=23E7ykoeZK&sig=TCGzHL11Dd1TrY1sd0hr_-iW8cc

Gottlieb, D., Redline, S., Nieto, J., Baldwin, C., Newman, A., Resnick, H., & Punjabi, N. (2006). Association of usual sleep duration with hypertension: the Sleep Heart Health Study. *Sleep*, *29*(8), 1009–1014. Retrieved from

https://www.researchgate.net/profile/Carol_Baldwin/publication/6843573_Association_of_usual_sleep_duration_with_hypertension_The_Sleep_Heart_Health_Study/links/00b7d522415afd7f74000000.pdf

Grandner, M. A., Kripke, D. F., Yoon, I. Y., & Youngstedt, S. D. (2006). Criterion validity of the Pittsburgh Sleep Quality Index: Investigation in a non-clinical sample. *Sleep and Biological Rhythms*, *4*(2), 129–136. doi:10.1111/j.1479-8425.2006.00207.x

Grandner, M. A., Patel, N. P., Gehrman, P. R., Perlis, M. L., & Pack, A. I. (2010). Problems Associated with Short Sleep: Bridging the Gap between Laboratory and Epidemiological Studies. *Sleep Medicine Reviews*, *14*(4), 239–247. doi:10.1016/j.smrv.2009.08.001.Problems

Gueorguieva, R., & Krystal, J. H. (2004). Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of General Psychiatry*, *61*(3), 310–317. doi:10.1001/archpsyc.61.3.310

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*, 145–73. doi:10.1146/annurev.psych.58.110405.085605

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm : Potential indices of risk in human development. *Development and Psychopathology*, *13*, 515–538.

Hakim, F., Wang, Y., Zhang, S., Zheng, J., Yolcu, E., Carreras, A., … Gozal, D. (2014). Fragmented sleep accelerates tumor growth and progression through recruitment of tumor-associated macrophages and TLR4 signaling. *Cancer Research*, *74*(5), 1329–1337.

Retrieved from https://cancerres.aacrjournals.org/content/74/5/1329.full

Harris, K., Spiegelhalder, K., Espie, C. A., MacMahon, K. M. A., Woods, H. C., & Kyle, S. D. (2015). Sleep-related attentional bias in insomnia: A state-of-the-science review. *Clinical Psychology Review*, *42*(AUGUST), 16–27. doi:10.1016/j.cpr.2015.08.001

Harvey, A. . (2002). A cognitive model of insomnia. *Behaviour Research and Therapy*, *40*(8), 869–893. doi:10.1016/S0005-7967(01)00061-4

Hatzinger, M., Brand, S., Perren, S., Stadelmann, S., von Wyl, A., von Klitzing, K., & Holsboer-Trachsler, E. (2008). Electroencephalographic sleep profiles and hypothalamic-pituitary-adrenocortical (HPA)-activity in kindergarten children: early indication of poor sleep quality associated with increased cortisol secretion. *Journal of Psychiatric Research*, *42*(7), 532–43. doi:10.1016/j.jpsychires.2007.05.010

Hewitt, P. L., Flett, G. L., & Mosher, S. W. (1992). The Perceived Stress Scale: Factor structure and relation to depression symptoms in a psychiatric sample. *Journal of Psychopathology and Behavioral Assessment*, *14*(3), 247–257. doi:10.1007/BF00962631

Horne, J., & Ostberg, O. (1975). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, *4*(2), 97–110. Retrieved from http://europepmc.org/abstract/med/1027738

Hruschka, D. J., Kohrt, B. a, & Worthman, C. M. (2005). Estimating between- and within-individual variation in cortisol levels using multilevel models. *Psychoneuroendocrinology*, *30*(7), 698–714. doi:10.1016/j.psyneuen.2005.03.002

Hsiao, F. H., Yang, T. T., Ho, R. T. H., Jow, G. M., Ng, S. M., Chan, C. L. W., … Wang, K. C.

(2010). The self-perceived symptom distress and health-related conditions associated with morning to evening diurnal cortisol patterns in outpatients with major depressive disorder. *Psychoneuroendocrinology*, *35*(4), 503–515. doi:10.1016/j.psyneuen.2009.08.019

Hu, P., Stylos-Allan, M., & Walker P., M. (2006). Sleep facilitates consolidatio of emotional declarative memory. *Psychological Science*, *17*(10), 891.

Ivanenko, A., Crabtree, V., Obrien, L., & Gozal, D. (2006). Sleep complaints and psychiatric symptoms in children evaluated at a pediatric mental health clinic. *Journal of Clinical Sleep Medicine*, *2*(1), 42–48. Retrieved from http://www.researchgate.net/profile/David_Gozal2/publication/6280324_Sleep_complaints_ and_psychiatric_symptoms_in_children_evaluated_at_a_pediatric_mental_health_clinic/lin ks/0912f5102e4d180733000000.pdf

Johns, M. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. Retrieved from http://epworthsleepinessscale.com/wp-content/uploads/2008/12/a-new-method-for-measuring-daytime-sleepiness-the-epworth-sleepiness-scale2.pdf

Johns, M. W. (1992). Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, *15*(4), 376–381.

Johnson, E., Kamilaris, T., Chrousos, G., & Gold, P. (1992). Mechanisms of stress: a dynamic overview of hormonal and behavioral homeostasis. *Neuroscience and Biobehavioral Reviews*, *16*(1), 115–130. Retrieved from http://www.sciencedirect.com/science/article/pii/S0149763405801757

85

Johnson, E. O., Roth, T., & Breslau, N. (2006). The association of insomnia with anxiety

disorders and depression: exploration of the direction of risk. *Journal of Psychiatric Research*, *40*(8), 700–8. doi:10.1016/j.jpsychires.2006.07.008

Joormann, J., & Gotlib, I. H. (2007). Selective attention to emotional faces following recovery

from depression. *Journal of Abnormal Psychology*, *116*(1), 80–5. doi:10.1037/0021-843X.116.1.80

Joormann, J., Talbot, L., & Gotlib, I. H. (2007). Biased processing of emotional information in

girls at risk for depression. *Journal of Abnormal Psychology*, *116*(1), 135–143. doi:10.1037/0021-843X.116.1.135

Kalsbeek, A., Spek, R. Van der, & Lei, J. (2012). Circadian rhythms in the hypothalamo–

pituitary–adrenal (HPA) axis. *Molecular and Cellular Endocrinology*, *349*(1), 20–29. Retrieved from http://www.sciencedirect.com/science/article/pii/S0303720711003753

Killgore, W. D. S., Kahn-Greene, E. T., Lipizzi, E. L., Newman, R. A., Kamimori, G. H., &

Balkin, T. J. (2008). Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep Medicine*, *9*(5), 517–526. doi:10.1016/j.sleep.2007.07.003

Killgore, W. D. S. S. (2010). *Effects of sleep deprivation on cognition*. (G. A. Kerkhof & H. P.

Van Dongen, Eds.)*Progress in Brain Research* (Vol. 185). Elsevier B.V. doi:10.1016/B978-0-444-53702-7.00007-5

Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999).

Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the

hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine*, *61*(2), 154–62. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10204967

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The "Trier Social Stress Test"--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*. doi:119004

Knutson, K. L., Spiegel, K., Penev, P., & Van Cauter, E. (2007). The metabolic consequences of sleep deprivation. *Sleep Medicine Reviews*, *11*(3), 163–178. doi:10.1016/j.smrv.2007.01.002

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a Brief Depression Severity Measure. *Journal of General Internal Medicine*, *16*(9), 606–613. doi:10.1046/j.1525-1497.2001.016009606.x

Krueger, P., & Friedman, E. (2009). Sleep duration in the United States: a cross-sectional population-based study. *American Journal of Epidemiology*. Retrieved from http://aje.oxfordjournals.org/content/169/9/1052.short

Kudielka, B. M., Buske-Kirschbaum, A., Hellhammer, D. H., & Kirschbaum, C. (2004). HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology*, *29*, 83–98. Retrieved from http://www.sciencedirect.com/science/article/pii/S0306453002001464

Kudielka, B. M., Federenko, I., Hellhammer, D. H., & Wüst, S. (2006). Morningness and eveningness: the free cortisol rise after awakening in "early birds" and "night owls". *Biological Psychology*, *72*(2), 141–146. doi:10.1016/j.biopsycho.2005.08.003

Kudielka, B. M., Hellhammer, D. H., & Kirschbaum, C. (2007). Ten years of research with the

    Trier Social Stress Test—revisited. In E. Harmon-Jones & P. Winkielman (Eds.), *Social*

    Neuroscience: Integrating biological and psychological explanations of social behavior (pp.

    56–83). New York: The Guilford Press. Retrieved from

    https://books.google.com/books?hl=en&lr=&id=mKSqxaHGaicC&oi=fnd&pg=PA56&dq=

    (Kudielka,+Hellhammer,+Kirschbaum,+2007)&ots=6UP9dn-rIa&sig=CDI37Nlm-jGt7d-

    tvKY92NxjbFQ

Kudielka, B. M., & Kirschbaum, C. (2003). Awakening cortisol responses are influenced by

    health status and awakening time but not by menstrual cycle phase.

    Psychoneuroendocrinology, *28*(1), 35–47. Retrieved from

    http://www.ncbi.nlm.nih.gov/pubmed/12445835

Kudielka, B. M., & Kirschbaum, C. (2005). Sex differences in HPA axis responses to stress: a

    review. *Biological Psychology*, *69*(1), 113–132. doi:10.1016/j.biopsycho.2004.11.009

Kudielka, B. M., Schommer, N., Hellhammer, D. H., & Kirschbaum, C. (2004). Acute HPA axis

    responses, heart rate, and mood changes to psychosocial stress (TSST) in humans at

    different times of day. *Psychoneuroendocrinology*, *29*, 983–992. Retrieved from

    http://www.sciencedirect.com/science/article/pii/S030645300300180X

Kumari, M., Badrick, E., Ferrie, J., Perski, A., Marmot, M., & Chandola, T. (2009). Self-reported

    sleep duration and sleep disturbance are independently associated with cortisol secretion in

    the Whitehall II study. *The Journal of Clinical Endocrinology and Metabolism*, *94*(12),

    4801–4809. doi:10.1210/jc.2009-0555

Kunz-Ebrecht, S. R., Kirschbaum, C., Marmot, M., & Steptoe, A. (2004). Differences in cortisol

awakening response on work days and weekends in women and men from the Whitehall II cohort. *Psychoneuroendocrinology*, *29*(4), 516–528. doi:10.1016/S0306-4530(03)00072-6

Lane, J. D. (2002). Caffeine Affects Cardiovascular and Neuroendocrine Activation at Work and Home. *Psychosomatic Medicine*, *64*(4), 595–603. doi:10.1097/01.PSY.0000021946.90613.DB

Lane, J. D., Adcock, R. a, Williams, R. B., & Kuhn, C. M. (1990). Caffeine effects on cardiovascular and neuroendocrine responses to acute psychosocial stress and their relationship to level of habitual caffeine consumption. *Psychosomatic Medicine*, *52*, 320–336. doi:10.1097/00006842-199005000-00006

Leproult, R., Copinschi, G., Buxton, O., & Van Cauter, E. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep*, *20*(10), 865–70. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9415946

Lewis, P. A., Cairney, S., Manning, L., & Critchley, H. D. (2011). The impact of overnight consolidation upon memory for emotional and neutral encoding contexts. *Neuropsychologia*, *49*(9), 2619–2629. doi:10.1016/j.neuropsychologia.2011.05.009

Lopez-Duran, N. L., Mayer, S. E., & Abelson, J. L. (2014). Modeling neuroendocrine stress reactivity in salivary cortisol: adjusting for peak latency variability. *Stress*. doi:10.3109/10253890.2014.915517

Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W., & Herzberg, P. Y. (2008). Validation and Standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. *Medical Care*, *46*, 266–274.

doi:10.1097/MLR.0b013e318160d093

MacLeod, C. M., Mathews, A., & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of Abnormal Psychology*, *95*(1), 15–20. doi:10.1037/0021-843X.95.1.15

Mai, E., & Buysse, D. J. (2008). Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation. *Sleep Medicine Clinics*, *3*(2), 167–174. doi:10.1016/j.jsmc.2008.02.001

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism*, *55*(10 Suppl 2), S20–23. doi:10.1016/j.metabol.2006.07.008

Meerlo, P., Koehl, M., van der Borght, K., & Turek, F. W. (2002). Sleep restriction alters the hypothalamic-pituitary-adrenal response to stress. *Journal of Neuroendocrinology*, *14*(5), 397–402. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12000545

Meerlo, P., Sgoifo, A., & Suchecki, D. (2008). Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews*, *12*(3), 197–210. doi:10.1016/j.smrv.2007.07.007

Meijer, J. H., Watanabe, K., Schaap, J., Albus, H., & Detari, L. (1998). Light Responsiveness of the Suprachiasmatic Nucleus : Long-Term Multiunit and Single-Unit Recordings in Freely Moving Rats. *Journal of Neuroscience*, *18*(21), 9078–9087.

Miller, R., & Plessow, F. (2013). Transformation techniques for cross-sectional and longitudinal endocrine data: application to salivary cortisol concentrations. *Psychoneuroendocrinology*, *38*(6), 941–946. doi:10.1016/j.psyneuen.2012.09.013

Mogg, K., & Bradley, B. P. (2005). Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognitive Therapy and Research*, *29*(1), 29–45. doi:10.1007/s10608-005-1646-y

Monk, T. H., Buysse, D. J., Reynolds, C. F., Berga, S. L., Jarrett, D. B., Begley, a E., & Kupfer, D. J. (1997). Circadian rhythms in human performance and mood under constant conditions. *Journal of Sleep Research*, *6*(1), 9–18. doi:10.1046/j.1365-2869.1997.00023.x

Morin, C. M. (1993). *Insomnia: Psychological Assessment and Management*. New York: Guilford Press. Retrieved from http://www.guilford.com/books/Insomnia/Charles-Morin/9781572301207/reviews

Morin, C. M., & Jarrin, D. C. (2013). Epidemiology of insomnia. *Sleep Medicine Clin*, *8*(3), 281–297. doi:10.1016/j.jsmc.2013.05.002

Morin, C. M., & Ware, J. C. (1996). Sleep and psychopathology. *Applied and Preventive Psychology*, *5*(4), 211–224. doi:10.1016/S0962-1849(96)80013-8

Nader, N., Chrousos, G., & Kino, T. (2010). Interactions of the circadian CLOCK system and the HPA axis. *Trends in Endocrinology & Metabolism*, *21*(5), 277–286. Retrieved from http://www.sciencedirect.com/science/article/pii/S1043276010000020

Ohayon, M. M. (2002). Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97–111. doi:10.1053/smrv.2002.0186

Orzeł-Gryglewska, J. (2010). Consequences of sleep deprivation. *International Journal of Occupational Medicine* …. Retrieved from http://www.degruyter.com/view/j/ijmh.2010.23.issue-1/v10001-010-0004-9/v10001-010-

0004-9.xml

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468. doi:10.1016/j.tins.2008.06.006

Payne, J. D., Chambers, A. M., & Kensinger, E. a. (2012). Sleep promotes lasting changes in selective memory for emotional scenes. *Frontiers in Integrative Neuroscience*, *6*(November), 108. doi:10.3389/fnint.2012.00108

Payne, J. D., & Kensinger, E. a. (2010). Sleep's role in the consolidation of emotional episodic memories. *Current Directions in Psychological Science*, *19*, 290–295. doi:10.1177/0963721410383978

Payne, J. D., Stickgold, R., Swanberg, K., & Kensinger, E. A. (2008). Sleep preferentially enhances memory for emotional components of scenes. *Psychological Science*, *19*(8), 781–788. doi:10.1111/j.1467-9280.2008.02157.x

Perlman, C., Johnson, S., & Mellman, T. (2006). The prospective impact of sleep duration on depression and mania. *Bipolar Disorders*. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1399-5618.2006.00330.x/pdf

Pesonen, A.-K., Kajantie, E., Heinonen, K., Pyhälä, R., Lahti, J., Jones, A., … Räikkönen, K. (2012). Sex-specific associations between sleep problems and hypothalamic-pituitary-adrenocortical axis activity in children. *Psychoneuroendocrinology*, *37*(2), 238–48. doi:10.1016/j.psyneuen.2011.06.008

Pilcher, J. J., & Horne, J. a. (1996). Effects of sleep deprivation on performance: A meta-analysis.

Sleep, *19*(4), 318–326.

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., Von Auer, K., Jobst,
S., … Kirschbaum, C. (1997). Free cortisol levels after awakening: A reliable biological
marker for the assessment of adrenocortical activity. *Life Sciences*, *61*(26), 2539–2549.

Räikkönen, K., Matthews, K. a, Pesonen, A.-K., Pyhälä, R., Paavonen, E. J., Feldt, K., …
Kajantie, E. (2010). Poor sleep and altered hypothalamic-pituitary-adrenocortical and
sympatho-adrenal-medullary system activity in children. *The Journal of Clinical
Endocrinology and Metabolism*, *95*(5), 2254–61. doi:10.1210/jc.2009-0943

Randler, C., & Schaal, S. (2010). Morningness-eveningness, habitual sleep-wake variables and
cortisol level. *Biological Psychology*, *85*(1), 14–18. doi:10.1016/j.biopsycho.2010.04.006

Ranjit, N., Young, E. A., Raghunathan, T. E., & Kaplan, G. A. (2005). Modeling cortisol
rhythms in a population-based study. *Psychoneuroendocrinology*, *30*(7), 615–624.
doi:10.1016/j.psyneuen.2005.02.003

Roberti, J. W., Harrington, L. N., & Storch, E. A. (2006). Further Psychometric Support for the
10-Item Version of the Perceived Stress Scale. *Journal of College Counseling*, *9*(2), 135–
147. doi:10.1002/j.2161-1882.2006.tb00100.x

Sadeh, A., & Gruber, R. (2002). Stress and sleep in adolescence: A clinical-developmental
perspective. In M. A. Carskadon (Ed.), *Adolescent sleep patterns: Biological, social, and
psychological influences* (pp. 236–253). New York: Cambridge University Press. Retrieved
from http://psycnet.apa.org/psycinfo/2003-04411-014

Sadeh, A., Keinan, G., & Daon, K. (2004). Effects of stress on sleep: the moderating role of

coping style. *Health Psychology*, *23*(5), 542–545. Retrieved from

http://psycnet.apa.org/journals/hea/23/5/542/

Sadeh, A., Sharkey, K., & Carskadon, M. (1994). Activity-Based Sleep—Wake Identification:

An Empirical Test of Methodological Issues. *Sleep*, *17*(3), 201–207. Retrieved from

http://www.researchgate.net/profile/Katherine_Sharkey/publication/15260355_Activity-

based_sleep-

wake_identification_an_empirical_test_of_methodological_issues/links/0deec52096766e6f

ab000000.pdf

Sagaspe, P., Sanchez-Ortuno, M., Charles, A., Taillard, J., Valtat, C., Bioulac, B., & Philip, P.

(2006). Effects of sleep deprivation on Color-Word, Emotional, and Specific Stroop

interference and on self-reported anxiety. *Brain and Cognition*, *60*(1), 76–87.

doi:10.1016/j.bandc.2005.10.001

Schmidt-Reinwald, A., Pruessner, J. C., Hellhammer, D. H., Federenko, I., Rohleder, N.,

Schurmeyer, T. H., & Kirschbaum, C. (1999). The Cortisol Response to Awakening in

Relation to Different Challenge Tests and a 12-Hour Cortisol Rhythm. *Life Sciences*, *64*(18),

1653–1660.

Sgoifo, A., Buwalda, B., Roos, M., Costoli, T., Merati, G., & Meerlo, P. (2006). Effects of sleep

deprivation on cardiac autonomic and pituitary-adrenocortical stress reactivity in rats.

Psychoneuroendocrinology, *31*(2), 197–208. doi:10.1016/j.psyneuen.2005.06.009

Spath-Schwalbe, E., Gofferje, M., Kern, W., Born, J., & Fehm, H. L. (1991). Sleep disruption

alters nocturnal ACTH and cortisol secretory patterns. *Biological Psychiatry*, *29*(6), 575–

584. doi:10.1016/0006-3223(91)90093-2

Spiegel, K., Knutson, K., Leproult, R., Tasali, E., & Van Cauter, E. (2005). Sleep loss: a novel

    risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology*, *99*,

    2008–2019. doi:10.1152/japplphysiol.00660.2005

Spiegelhalder, K., Espie, C., & Riemann, D. (2009). Is sleep-related attentional bias due to

    sleepiness or sleeplessness? *Cognition and Emotion*, *23*(February 2012), 541–550.

    doi:10.1080/02699930802022129

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for

    assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine*, *166*(10),

    1092–1097. Retrieved from http://archpedi.jamanetwork.com/article.aspx?articleid=410326

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wust, S., … Clow,

    A. (2015). Assessment of the cortisol awakening response: Expert consensus guidelines.

    Psychoneuroendocrinology.

Steiger, A. (2002). Sleep and the hypothalamo–pituitary–adrenocortical system. *Sleep Medicine*

    Reviews, *6*(2), 125–138. doi:10.1053/smrv.2001.0159

Stepanski, E., Zorick, F., Roehrs, T., & Roth, T. (2000). Effects of sleep deprivation on daytime

    sleepiness in primary insomnia. *Sleep*, *23*(2), 215–9. Retrieved from

    http://europepmc.org/abstract/med/10737338

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature*, *437*(7063), 1272–8.

    doi:10.1038/nature04286

Stroud, L. R., Salovey, P., & Epel, E. S. (2002). Sex differences in stress responses: Social

    rejection versus achievement stress. *Biological Psychiatry*, *52*(4), 318–327.

doi:10.1016/S0006-3223(02)01333-1

Treuer, K., Norman, T. R., & Armstrong, S. M. (2007). Overnight human plasma melatonin,
cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep
recovery. *Journal of Pineal Research*, *20*(1), 7–14. Retrieved from
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-079X.1996.tb00232.x/full

Tsai, P. S., Wang, S. Y., Wang, M. Y., Su, C. T., Yang, T. T., Huang, C. J., & Fang, S. C. (2005).
Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index
(CPSQI) in primary insomnia and control subjects. *Quality of Life Research*, *14*(8), 1943–
1952. doi:10.1007/s11136-005-4346-x

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine
factors and stress. *Journal of Psychosomatic Research*, *53*(4), 865–71. Retrieved from
http://www.ncbi.nlm.nih.gov/pubmed/12377295

Ustinov, Y., Lichstein, K. L., Wal, G. S. Vander, Taylor, D. J., Riedel, B. W., & Bush, A. J.
(2010). Association between report of insomnia and daytime functioning. *Sleep Medicine*,
11(1), 65–8. doi:10.1016/j.sleep.2009.07.009

Van Cauter, E., Leproult, R., & Kupfer, D. J. (1996). Effects of gender and age on the levels and
circadian rhythmicity of plasma cortisol. *The Journal of Clinical Endocrinology &
Metabolism*, *81*(7), 2468–2473. Retrieved from
http://press.endocrine.org/doi/abs/10.1210/jcem.81.7.8675562

Vargas, I., & Lopez-Duran, N. L. (2014). Dissecting the impact of sleep and stress on the cortisol
awakening response among healthy young adults. *Psychoneuroendocrinology*, *40*(1), 10–16.

Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24485471

Vgontzas, A., Mastorakos, G., Bixler, E. O., Kales, A., Gold, P. W., & Chrousos, G. P. (1999). Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clinical Endocrinology*, *51*(2), 205–215. doi:cen763 [pii]

Vgontzas, A. N., Bixler, E. O., Lin, H. M., Prolo, P., Mastorakos, G., Vela-Bueno, A., & Chrousos, G. P. (2001). Chronic Insomnia Is Associated with Nyctohemeral Activation of the Hypothalamic-Pituitary-Adrenal Axis: Clinical Implications. *The Journal of Clinical Endocrinology & Metabolism*, *86*(8), 3787–3794.

Vrshek-Schallhorn, S., Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2013). The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. *Psychological Medicine*, *43*(3), 483–493. doi:10.1017/S0033291712001213

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learning & Memory*. Retrieved from http://learnmem.cshlp.org/content/8/2/112.short

Watson, D., Clark, L., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. Retrieved from http://psycnet.apa.org/psycinfo/1988-31508-001

Wehr, T. (1998). Effect of seasonal changes in daylength on human neuroendocrine function.

Hormone Research in Paediatrics. Retrieved from

http://www.karger.com/Article/Abstract/23157

Wilhelm, I., Born, J., Kudielka, B. M., Schlotz, W., & Wüst, S. (2007). Is the cortisol awakening

rise a response to awakening? *Psychoneuroendocrinology*, *32*(4), 358–366.

doi:10.1016/j.psyneuen.2007.01.008

Williams, L. S., Brizendine, E. J., Plue, L., Bakas, T., Tu, W., Hendrie, H., & Kroenke, K.

(2005). Performance of the PHQ-9 as a screening tool for depression after stroke. *Stroke*,

36(3), 635–8. doi:10.1161/01.STR.0000155688.18207.33

Wingenfeld, K., Terfehr, K., Meyer, B., Löwe, B., & Spitzer, C. (2012). Memory bias for

emotional and illness-related words in patients with depression, anxiety and somatization

disorders: an investigation with the directed forgetting task. *Psychopathology*. Retrieved

from http://www.karger.com/Article/Fulltext/338609

Winget, C. M., Deroshia, C. W., Markley, C. L., & Holley, D. C. (1984). A review of human

physiological and performance changes associated with desynchronosis of biological

rhythms. *Aviation, Space, and Environmental Medicine*, *55*(12), 1085–1096. Retrieved from

http://www.dailyairlinefilings.com/faapdf2/317.pdf

Wright, C. E., Valdimarsdottir, H. B., Erblich, J., & Bovbjerg, D. H. (2007). Poor sleep the night

before an experimental stress task is associated with reduced cortisol reactivity in healthy

women. *Biological Psychology*, *74*(3), 319–27. doi:10.1016/j.biopsycho.2006.08.003

Wüst, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors,

perceived chronic stress, and the free cortisol response to awakening.

Psychoneuroendocrinology, *25*(7), 707–20. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/10938450

Yoo, S.-S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain

without sleep--a prefrontal amygdala disconnect. *Current Biology*, *17*(20), R877–8.

doi:10.1016/j.cub.2007.08.007

Young, E. A., Abelson, J. L., & Cameron, O. G. (2004). Effect of comorbid anxiety disorders on

the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression.

Biological Psychiatry, *56*(2), 113–120. doi:10.1016/j.biopsych.2004.03.017

Zhang, J., Ma, R., Kong, A., So, W., Li, A., Lam, S., … Wing, Y. (2011). Relationship of sleep

quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in

healthy middle-aged adults. *Sleep*, *34*(2), 225–233. Retrieved from

https://www.researchgate.net/profile/Ronald_Ma/publication/49802992_Relationship_of_sl

eep_quantity_and_quality_with_24-

hour_urinary_catecholamines_and_salivary_awakening_cortisol_in_healthy_middle-

aged_adults/links/00b49522de752cf3ca000000.pdf