Investigating the effect of acute sleep deprivation on hypothalamic-pituitary-adrenal-axis response to a psychosocial stressor

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A R T I C L E   I N F O

Article history:
Received 8 August 2016
Received in revised form 23 January 2017
Accepted 25 January 2017

Keywords:
Sleep
Stress
HPA axis
Cortisol
Sleep deprivation
Gender

A B S T R A C T

The hypothalamic-pituitary-adrenal (HPA) axis has been previously identified as one potential mechanism that may explain the link between sleep deprivation and negative health outcomes. However, few studies have examined the direct association between sleep deprivation and HPA-axis functioning, particularly in the context of stress. Therefore, the aim of the current study was to investigate the relationship between acute sleep deprivation and HPA-axis reactivity to a psychosocial stressor. Participants included 40 healthy, young adults between the ages of 18–29. The current protocol included spending two nights in the laboratory. After an adaptation night (night 1), participants were randomized into either a sleep deprivation condition (29 consecutive hours awake) or a control condition (night 2). Following the second night, all participants completed the Trier Social Stress Test (TSST). Salivary cortisol was collected before, during, and after the TSST. Results indicated that there were significant group differences in cortisol stress reactivity. Specifically, compared to participants in the control condition, participants in the sleep deprivation condition had greater baseline (i.e., pre-stress) cortisol, yet a blunted cortisol response to the TSST. Taken together, a combination of elevated baseline cortisol (and its subsequent effect on HPA-axis regulatory processes) and a relative ‘ceiling’ on the amount of cortisol a laboratory stressor can produce may explain why participants in the sleep deprivation condition demonstrated blunted cortisol responses.

1. Introduction

While individual sleep need varies widely from person to person, most sleep experts recommend 7 to 9 h of sleep per night (Hirshkowitz et al., 2015). Yet, nearly 30% of adults sleep 6 or fewer hours per night (Krueger and Friedman, 2009). These rates are concerning as sleep deprivation is linked to a number of negative health outcomes, including psychiatric (Breslau et al., 1996), metabolic (Knutson et al., 2007), and cardiovascular problems (Grandner et al., 2013). However, the actual mechanisms by which sleep deprivation impacts health are relatively unknown. Growing research points to variability in neuroendocrine functioning, in particular the hypothalamic-pituitary-adrenal (HPA) axis, as a potential mechanism by which sleep deprivation leads to poor health (Balbo et al., 2010; Meerlo et al., 2008). Yet, experimental studies on the association between sleep deprivation and HPA-axis functioning, in particular cortisol stress reactivity, are limited (Minkel et al., 2014). Accordingly, the current study explored the link between acute sleep deprivation and HPA-axis stress reactivity under controlled conditions.

The HPA axis’ primary function is to regulate physiological responses to stress (de Kloet, 1991; Johnson et al., 1992). HPA-axis stress reactivity is, however, also modulated by several individual (e.g., age, gender; Kudielka et al., 2004a) and contextual factors (e.g., time of day; Kudielka et al., 2004b). Among these factors, sleep may play a critical role in modulating HPA-axis stress reactivity (Sgoifo et al., 2006). Several studies suggest that poor sleep is associated with atypical cortisol reactivity to psychosocial stress among both children (Hatzinger et al., 2008; Raikkonen et al., 2010) and adults (Wright et al., 2007). Specifically, poor self-reported sleep quality has been linked to elevated cortisol responses to a laboratory stress task (Goodin et al., 2012). Similarly, among children and adolescents...
cents, lower objective (e.g., lower sleep efficiency, more time spent in ‘light’ stages of sleep) and subjective sleep quality predicted greater overall cortisol production in response to stress (Hatzinger et al., 2008; Mrug et al., 2016; Raikkonen et al., 2010). A more recent study among a small sample of healthy adults used an experimental paradigm to demonstrate a link between acute (i.e., total) sleep deprivation and elevated cortisol responses to a laboratory stressor (Minkel et al., 2014). Poor or insufficient sleep may increase adrenal sensitivity, and thus exacerbate cortisol production during acute stress. For example, following a 48 h sleep deprivation protocol, sleep deprived rodents showed blunted adrenocorticotrophic hormone (ACTH) compared to controls, 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.

Alternatively, other studies have demonstrated a link between poor sleep and a blunted cortisol response to acute stress (Capaldi et al., 2005; Wright et al., 2007). These inconsistencies further highlight the need to identify the specific mechanisms by which poor sleep is responsible for atypical HPA-axis functioning. For example, poor sleep may be due to elevated physical or mental health symptoms that may be differentially related to high and low stress reactivity. However, to date, only one study has examined the impact of experimental sleep deprivation among humans (Minkel et al., 2014), and therefore, it is relatively unknown whether sleep deprivation actually leads to differences in HPA-axis stress reactivity. Addressing this question is important because it is possible that sleep deprivation and HPA-axis functioning are not directly related and are instead due to a third variable, such as high levels of stress (Sadeh and Gruber, 2002; Sadeh et al., 2004) or the presence of comorbid psychiatric symptoms (Ivanenko et al., 2006). However, experimentally controlled sleep deprivation has been consistently linked to elevated circadian cortisol (i.e., greater nocturnal cortisol during sleep deprivation and higher post-deprivation evening cortisol; Leproult et al., 1997; Treuer et al., 2007), and thus it is possible that sleep deprivation directly impacts other indices of HPA-axis functioning (e.g., stress reactivity) as well.

Therefore, the current study investigated the relationship between total sleep deprivation and HPA-axis stress reactivity under experimental conditions. We hypothesized that sleep deprivation would be associated with greater cortisol in response to stress, given the demonstrated links between poor sleep and increased HPA-axis stress reactivity (Goodin et al., 2012; Hatzinger et al., 2008; Raikkonen et al., 2010). Specifically, we aimed to extend Minkel et al.’s (2014) findings and provide further support for the link between acute sleep deprivation and HPA-axis sensitivity to stress, which may have treatment implications for a variety of conditions linked to an elevated cortisol stress response (e.g., depression; Burke et al., 2005).

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 of a mid-size city in the United States. Participants were recruited through online and printed advertisements placed in local businesses and community centers seeking “healthy” young adults for a sleep study. Participants were ineligible for participation if they were (1) pregnant, (2) taking any medication that impacts endocrine functioning, (3) previously diagnosed with a chronic medical condition (e.g., sleep apnea, cancer, lupus, diabetes), endocrine disorder (e.g., Cushing’s syndrome, Addison’s disease), or a psychiatric disorder (including insomnia), or (4) unable to maintain a regular sleep cycle during the week prior to the overnight visits (e.g., shift worker). All participants were able to maintain a regular sleep cycle, and therefore, no participants were excluded for this reason. 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). There were no significant differences between the five participants who did not complete the study and the remaining sample on age (F = 0.34, p > 0.20), depressive symptomatology (F = 1.15, p > 0.20), perceived stress (F = 0.59, p > 0.20), life events (F = 1.78, p = 0.19), insomnia symptoms (F = 0.12, p > 0.20), daytime sleepiness (F = 0.04, p > 0.20), self-reported habitual sleep quality (F = 0.05, p > 0.20), or chronobiological preference (F = 1.29, p > 0.20). The majority of participants in the final sample identified as Caucasian (57.5%). 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. 75% of the sample included full-time college students (undergraduate or graduate students). The Institutional Review Board of a large American research university approved the study, and participants signed a written informed consent.

2.2. Procedures

2.2.1. 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 et al., 1989), daytime sleepiness (Epworth Sleepiness Scale; Johns, 1991), chronobiological preference (Morningness–Eveningness Questionnaire; Horne and Ostberg, 1976), and insomnia symptoms (Insomnia Severity Index; Morin, 1993). Participants also completed a general demographic questionnaire that included other sleep–related information (e.g., habitual caffeine use). Following the baseline visit, participants wore an actigraphy device (Actiwatch 2, Philips – RespiroNics) on their non-dominant wrist for approximately seven days (range = 2–11 days). The actigraph is a widely used method for objectively assessing daily sleep/wake patterns (Sadeh et al., 1994). In addition, on each day actigraphy data was collected, participants were asked to complete a brief online sleep diary (modified Consensus Sleep Diary; Carney et al., 2012). Participants were instructed to maintain a regular sleep/wake schedule (i.e., 7–8 h of sleep per night; morning waking time between 06:00-09:00) and abstain from napping during the subsequent week. Actigraphy and sleep diary data were used to estimate each participant’s habitual (i.e., average) sleep patterns during the week prior to the overnight laboratory visit. While not all participants were able to provide a week’s worth of actigraphy and diary data due to scheduling limitations, there were no significant difference in the number of days collected between conditions, F = 0.003, p > 0.20; sleep deprivation, M_days = 7.32, sleep controls, M_days = 7.35. The adaptation night was not included in these estimates since they were given a predetermined bed and rise time. Sleep efficiency, total sleep time, and other sleep continuity variables (e.g., wake after sleep onset, nocturnal awakenings) are sensitive to first night effects (Agnew et al., 1966), and therefore, not representative of habitual sleep patterns. Notably, there were no significant group differences on any of the actigraphy–measured sleep variables during the adaptation night. The following sleep parameters were used as covariates for the current analyses: total sleep time (TST), sleep efficiency (SE), sleep onset latency (SL; 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 (NWAK; number of awakenings).
Specifically, samples were obtained for 15 min prior to assay, which was done using duplicates with 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.

2.3.2. Other covariates

Participants also completed additional self-report measures to control for depressive symptoms, anxiety, stress, and affect. Depressive symptoms were assessed via the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001). The Generalized Anxiety Disorder Screener (GAD-7; Spitzer et al., 2006) was used to assess anxiety and worry. The Perceived Stress Scale (PSS; Cohen et al., 1983) was used to assess current perceived stress, whereas the Psychiatric Epidemiology Research Interview – Life Events Scale (PERI-LES; Dohrenwend et al., 1978) was used to assess exposure to stress during the past six months. The Positive and Negative Affect Scale (PANAS; Watson et al., 1988) was used to assess positive and negative affect. The PANAS was completed the morning after the experimental manipulation, within one hour of awakening (for the control condition) or between 08:00–09:00 (for the sleep-deprived condition). All other questionnaires were completed during the adaptation night (prior to going to sleep).

2.4. Statistical analysis

We used multiple adjusted random effects growth curve models via SPSS MIXED to examine the association between the experimental condition and cortisol stress trajectories. Specifically, we examined the effect of condition on pre-stress, baseline cortisol (intercept) and cortisol reactivity (non-linear 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 and Krystal, 2004; Hruschka et al., 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, particularly in small samples (Lopez-Duran et al., 2014). All models included intercept and reactivity slopes as random effects within subjects and used an unstructured covariance structure to allow for best fit to the data. Extreme cortisol samples at the upper 2% of the distribution (>1.00 μg/dL; 9 of 439 samples) were winsorized (i.e. the top 2 percentile values were recorded and set at the 98th percentile value). To correct for skewness, cortisol data were transformed using a Box-Cox transformation (λ = −0.33; Miller and Plessow, 2013). All other skewed data were log-transformed. Continuous variables were mean-centered to ease interpretation.

3. Results

3.1. Descriptive statistics

Table 1 presents group means and standard deviations of all baseline variables. There were significant group differences for a number of variables. Specifically, relative to participants in the control condition, participants in the sleep deprivation condition reported significantly greater perceived stress (i.e., PSS), F = 6.16, p = 0.02, and a shorter average total sleep time (TST), F = 5.67, p = 0.02, during the baseline week prior to the experimental visit. Notably, there were no significant differences in habitual caffeine use between groups, F = 0.704, p > 0.20. 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; 66%) were currently using at least one form of contraceptive. Not surprisingly, compared to participants in the control condition, participants in the sleep deprivation condition 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 manipulation (prior to the TSST; see Table 2 for mean comparisons).

3.2. Unadjusted effect of experimental condition on cortisol stress reactivity

Based on independent t-tests, there was a significant group difference in baseline cortisol (−10 min pre-stress), F = 4.76, p = 0.035, but no differences in cortisol at any other time point (Table 2). Next we conducted unconditional growth curve models to examine the overall cortisol stress response across both conditions. Modeling cortisol reactivity alone suggested that cortisol increased linearly from baseline (−10 min pre-stress), time b = 0.065, t(259) = 13.4, p < 0.001, but there was a significant deceleration of this increase over time, timeb 2 = −0.0007, t(358) = −12.3, p < 0.001, 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).

We then computed an unadjusted model to examine the effect of condition (i.e., sleep deprivation versus control) on cortisol stress reactivity. Results from our unadjusted model indicated significant differences between our two experimental conditions. Specifically, compared to participants in the control condition, participants in the sleep deprivation condition had greater baseline cortisol (i.e., pre-stress cortisol), condition b = 0.727, t(45) = 2.20, Δ% = 21.2, p = 0.03, yet a blunted cortisol response, condition x time b = −0.026, t(251) = −2.66, Δ% = −32.9, p = 0.01, condition x time2 b = 0.0003, t(357) = 2.52, Δ% = 33.9, p = 0.01. These data suggest that 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 (Fig. 2).

3.3. Covariates and adjusted effect of experimental condition on cortisol stress reactivity

We next examined whether the effect of condition remained significant while controlling for gender, habitual caffeine use, perceived stress (PSS), average total sleep time (TST), and positive (PA) and negative (NA) affect. We included gender and caffeine use in the final analyses given their previously observed link to cortisol stress reactivity (Al’Absi et al., 1998; Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2005; Lane et al., 1990; Lane, 2002). We included the remaining covariates in the final analyses given the significant group differences reported above. No other covariates were included in the final analyses. In order to maximize the power to detect differences, we first estimated the effect of condition on cortisol stress reactivity while controlling for each covariate separately. The condition effect remained significant while controlling for each covariate separately (see Table 3 for model estimates). Furthermore, gender, habitual caffeine use, PA, and NA were also independently associated with cortisol stress reactivity. We next computed a final adjusted model where all covariates that were significantly associated with cortisol reactivity were included. In the final, adjusted model, our results confirmed that participants in the sleep deprivation condition had greater baseline cortisol, condition b = 0.797, t(38) = 1.82, Δ% = 23.0, p = 0.08, yet a blunted cortisol stress response, compared to participants in the control condition, condition x time b = −0.029, t(199) = −2.26, Δ% = −28.8, p = 0.03, condition x time2
4. Discussion

Despite studies indicating that sleep deprivation is associated with differences in HPA-axis functioning (Meerlo et al., 2002; Meerlo et al., 2008), few studies have examined whether experimental sleep deprivation is associated with HPA-axis functioning, especially under stressful conditions (Leproult et al., 1997; Minkel et al., 2014; Treuer et al., 2007). The aim of the current study was to investigate whether acute sleep deprivation led to differences in HPA-axis reactivity to 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 deprivation has been previously linked to elevated HPA-axis functioning (Leproult et al., 1997; Meerlo et al., 2008; Minkel et al., 2014). We found the opposite: participants in the sleep deprivation condition had greater baseline (i.e., pre-stress) cortisol and a blunted cortisol response to the stressor compared to their non-sleep-deprived peers.

Consistent with previous studies (i.e., Leproult et al., 1997; Minkel et al., 2014), sleep deprivation was associated with elevated baseline (i.e., pre-stress) cortisol, and thus, further supports that acute sleep loss may alter daytime cortisol among healthy, young adults during the subsequent day (please note: this effect only reached trend-level significance [p < 0.10] while controlling for covariates in our adjusted model and not the conventional p < 0.05 significance level). While the diurnal rhythm of most physiological systems is relatively stable (Czeisler et al., 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 and Steptoe, 2009; Elder et al., 2013). Greater cortisol activation following acute sleep deprivation may serve important 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 and Quevedo, 2007).

In contrast to our hypotheses and previous research (Minkel et al., 2014), sleep deprivation was not associated with greater cortisol reactivity to an acute psychosocial stressor. Instead, participants in the control condition had a significantly stronger cortisol response to the TSST compared to those in the sleep deprivation condition. It is possible that differences in baseline levels had an effect on the intensity of the stress response. Specifically, 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 a self-regulatory feedback system to shutdown the HPA axis (Buckley and Schatzberg, 2005; Gunnar and Vazquez, 2001). If high baseline cortisol is 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 participants 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 TSST.

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 in response to stress. Taken together, a combination of high start-

$b = 0.0003, t(335) = 2.65, \%\Delta = 34.2, p < 0.01$. Gender and habitual caffeine use were also independently associated with cortisol stress reactivity. Specifically, compared to females, males showed a greater cortisol response to the TSST, $b = 0.29, t(38) = 0.80, \%\Delta = 3.3, p > 0.20$, sex x time $b = 0.03, t(199) = 2.73, \%\Delta = 28.5, p < 0.01$, sex x time$^2 b = 0.0003, t(335) = 2.82, \%\Delta = 29.8, p < 0.01$ (Fig. 3). Similarly, compared to participants who reported no caffeine use, caffeine users showed a greater cortisol response to the TSST, $b = 0.17, t(38) = 1.40, \%\Delta = 18.0, p = 0.01$, caffeine x time $b = 0.03, t(199) = 2.31, \%\Delta = 29.9, p < 0.05$, caffeine x time$^2 b = 0.0004, t(335) = 2.72, \%\Delta = 35.7, p < 0.01$.

![Fig. 2. Estimated, unadjusted effect of experimental condition on cortisol response to the TSST.](image-url)
ing values and a ‘ceiling effect’ may explain why participants in the sleep deprivation condition demonstrated a blunted cortisol stress response. The current findings, however, are not consistent with Minkel et al.’s (2014) recent data suggesting that acute sleep deprivation was associated with an amplified cortisol stress response to the TSST. There are a number of important methodological differences (i.e., age of sample, time of stressor/collection, sampling rate, and statistical approach) between the two studies, but a key difference is that the peak cortisol change from baseline in their sleep control group was minimal (+30 min post-stress change among control group: current study = 0.26 μg/dL; Minkel et al. = −0.10 μg/dL). While the specific reason for this difference is unknown, there are a number of potential explanations, most notably, differences in the age of the sample (Mage: current study = 22.7 years; Minkel et al. = 34.9 years). Prior research suggests that younger adults have a greater endocrine response to the TSST relative to older adults (Kudielka et al., 2004a,b), and therefore, it is possible that the older adults in the control condition buffered the overall cortisol stress response (Minkel et al., 2014). In contrast, the current findings are consistent with other studies that have demonstrated a link between poor sleep quality and a blunted cortisol response to acute stress. It is difficult, however, to integrate these findings given that these prior studies were limited to self-reported and actigraph-based habitual sleep quality among children (Capaldi et al., 2005) and women (Wright et al., 2007).

These findings should be considered in the context of a number of study strengths and limitations. The current study used a dense sampling procedure and a growth curve modeling framework which addresses the limitations of more traditional approaches when examining repeated neuroendocrine data (e.g., AUC, repeated-measures ANOVA; Guerguieva and Krystal, 2004; Hruschka et al., 2005). In fact, 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. Our analyses also included a number of potentially confounding variables (e.g., gender, caffeine use, habitual sleep patterns, baseline stress, mood/affect etc.). Including these covariates in our models allows us to demonstrate the robustness of the independent association between sleep deprivation and cortisol reactivity.

While the current study provides support for the 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 also 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. Furthermore, acute sleep deprivation (i.e., one night of total sleep deprivation) has limited ecological validity, but given that there is minimal research on this topic, it was a logical first step. Future studies that compare the differential impact of various types of sleep loss (e.g., REM sleep deprivation, chronic 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, the current study only assesses cortisol stress reactivity at a single time point (i.e., post experimental manipulation). While studies suggest there is significant within-subject variability in cortisol levels (Hruschka et al., 2005), the TSST is sensitive to habituation or practice effects (Kudielka et al., 2007). Future studies, should replicate the current findings using an alternative laboratory stressor that is less sensitive to practice effects (e.g., cold press task), and therefore, can be assessed repeatedly. While there may also be concerns that the TSST was administered earlier than standard recommendations (Dickerson and Kemeny, 2004), previous research reported similar peak salivary cortisol increases following the TSST during morning (09:00–10:00) and afternoon (15:00–16:00) sessions, suggesting that cortisol responses to the TSST can be assessed as early as 09:00–10:00 (Kudielka et al., 2004b). 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 and 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 influence the primary aim of the current study. 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

![Fig. 3. Estimated, adjusted effect of gender on cortisol response to the TSST.](image-url)
large (range = 18–29, M\text{age} = 22.7, SD\text{age} = 3.1) and not a traditional “college sample”. Nonetheless, subsequent studies should examine factors that impact cortisol stress reactivity among more heterogeneous samples, including clinical populations.

In conclusion, the current study advances our understanding of the link between sleep deprivation and HPA-axis stress reactivity. Specifically, this was the first study to use a carefully controlled sleep manipulation to examine whether sleep deprivation was associated with cortisol reactivity to a widely used laboratory stress task (i.e., TSST). Our findings further supported the view that sleep deprivation has an effect on daytime cortisol (i.e., elevated baseline cortisol). Yet, sleep deprivation may have the opposite effect on cortisol reactivity to stress, at least among healthy populations. These results may also have important implications for understanding the factors that confer risk for negative health outcomes (e.g., depression; Breslau et al., 1996). For example, while depression has been linked to differences in cortisol stress reactivity, the results have been mixed, with reports indicating that depression is associated with both elevated and blunted cortisol response to stress (Burke et al., 2005). The current findings support the view that sleep deprivation may account for these discrepant results and that future research investigating the relationship between depression and HPA-axis stress reactivity should account for variability in sleep during the night prior to exposing participants to stress.

Role of the funding source

Funding for this research was provided by the University of Michigan Department of Psychology, University of Michigan Rackham Graduate School, Blue Cross Blue Shield of Michigan Foundation, and the American Psychological Association of Graduate Students. All grants were awarded to Dr. Ivan Vargas. The funding source had no role in the study design, data collection, analyses, or manuscript preparation.

Acknowledgements

The authors would like to thank the Michigan Psychoneuroendocrinology Affective Laboratory staff, particularly Andrew Garon, Rebecca Mulder, Tonia Ballantyne, Lara Favaz, Allie Hammond, and Rachel Cannon who assisted in data collection. Finally, we thank Dr. Christopher Drake for providing useful feedback during the study development phase.

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