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# EFFECTS OF SLEEP RESTRICTION ON APPETITIVE DESIRE, THREAT DISCRIMINATION, AND INCENTIVE-MODULATED INHIBITORY CONTROL

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## ABSTRACT

Sleep is critical for optimal cognitive and affective functioning, yet approximately one-third of U.S. adults receives fewer than the recommended 7 hours of sleep per night. Much of what is known about the impact of sleep loss on human functioning, particularly at the level of brain function, has been revealed through studies of acute total sleep deprivation for one night. However, few studies have involved multiple nights of partial sleep restriction, which may be more reflective of the typical U.S. adult obtaining insufficient sleep across the work week. Therefore, this study evaluated neurobehavioral performance in 15 healthy male participants following five nights with five hours of time in bed per night. Neurobehavioral measures were compared within-participants against a rested baseline condition (three nights with ten hours' time in bed per night) and a subsequent recovery condition (two nights with ten hours' time in bed per night). Participants completed three tasks while undergoing functional magnetic resonance imaging (fMRI) at baseline, after four nights of sleep restriction, and after one night of recovery sleep. First, a food desirability task evaluated participants' appetitive desire for a variety of food images. Previous research has shown an enhanced preference for calorie-dense over calorie-sparse foods, as well as a reduction in activity in brain networks involved in appetitive evaluation, following a single night of total sleep deprivation. Second, a social threat discrimination task assessed participants' perception of emotional faces, which they categorized as either threatening or not threatening. Research has previously demonstrated greater sensitivity to threatening faces and a decoupling of central brain networks from peripheral affective cues following one night of total sleep deprivation. Lastly, an incentive-modulated

antisaccade task instructed participants to execute targeted oculomotor movements, while inhibiting off-target movements, during reward, loss, and neutral trials. Although no other sleep study has used this task in conjunction with neuroimaging, there is a well-established link between short sleep duration and diminished inhibitory control, particularly as it manifests in risk-taking behavior. Outside the scanner, participants completed a risk-taking task approximately every two hours of the study, and they completed appetite questionnaires before every meal. Across all assessments, it was hypothesized that neurobehavioral performance and brain function would show similar changes as had previously been reported in studies involving one night of total sleep deprivation.

Results generally did not support the hypotheses on most measures. From the fMRI, only two regions of interest showed any change between the rested baseline and sleep restriction conditions. First, the right ventral striatum became more responsive during reward relative to neutral trials on the antisaccade task during the sleep-restricted condition. This finding is consistent with reports from previous sleep studies of incentive-modulated inhibitory control following one night of total sleep deprivation, and it may reflect alterations in reward processing connected to substance use and risk-taking. Accordingly, risk-taking behavior was found to increase during sleep restriction compared to baseline when assessed on a separate risk-taking task outside the scanner. Second, the anterior cingulate became less responsive to desired food images following four nights of partial sleep restriction. This is consistent with previous findings that sleep-deprived individuals rely less on deliberative processes associated with the anterior cingulate when considering the desirability of food stimuli. On neurobehavioral

measures, however, some results directly contradicted the hypotheses. Participants exhibited an unexpected decrease in sensitivity to threatening faces on the social threat discrimination task. Likewise, participants showed an unexpected preference for calorie-sparse over calorie-dense foods on every day of the study, and they reported a reduced preference for calorie-dense foods during sleep restriction. Because this reduced preference was only observed on the preprandial questionnaires but not the food desirability task, this might mean that participants evaluate their options differently when they are shown images of the food options and are told they will be rewarded with a highly desired food item based on their responses. These findings should be cautiously interpreted in the context of a small sample comprised of only male participants. Future studies are needed to investigate the effects of partial sleep restriction on brain function and neurobehavioral measures in larger, gender-balanced samples.

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## LIST OF ABBREVIATIONS

2-AG = 2-arachidonoylglycerol

ACC = anterior cingulate cortex

AFNI = Analysis of Functional NeuroImages software package

ANOVA = analysis of variance

BA = Brodmann area

BART = Balloon Analog Risk Task

BMI = body mass index

BOLD = blood oxygen level-dependent

CI = confidence interval

CRC = Pennsylvania State University Clinical Research Center

DACC = dorsal anterior cingulate cortex

DAT = dopamine transporter

DLPFC = dorsolateral prefrontal cortex

DMPFC = dorsomedial prefrontal cortex

EEG = electroencephalogram

EPI = echo planar imaging

EVAR = Evaluation of Risks

FEF = frontal eye field

fMRI = functional magnetic resonance imaging

FOV = field of view

FWE = family-wise error

IGT = Iowa Gambling Task

IPL = inferior parietal lobule

IPS = intraparietal sulcus

LCT = Lottery Choice Task

MPFC = medial prefrontal cortex

MPRAGE = magnetization prepared rapid gradient echo

MRI = magnetic resonance imaging

OFC = orbitofrontal cortex

PANAS = Positive Affect and Negative Affect Scales

PET = positron emission tomography

PPC = posterior parietal cortex

PSG = polysomnography

PSQI = Pittsburgh Sleep Quality Index

PVT = Psychomotor Vigilance Task

ROI = region of interest

SD = standard deviation

SEF = supplementary eye field

SEM = standard error of the mean

SMA = supplementary motor area

SPL = superior parietal lobule

TE = echo time

TIB = time in bed

TR = repetition time

VMPFC = ventromedial prefrontal cortex

VTA = ventral tegmental area

*Common Abbreviations…*

3D = three-dimensional

3T = three Tesla

Ca = calcium

h = hours

Hz = hertz

K = potassium

kcal = kilocalories

kg = kilograms

m = meters

mm = millimeters

mEq = milliequivalent

mg = milligrams

ms = milliseconds

Na = sodium

sec = seconds

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For Grandma.

# Chapter 1. Introduction

## Sleep & Neurobehavioral Function

Adequate sleep, according to a joint consensus by the American Academy of Sleep Medicine and the Sleep Research Society, means 7 or more hours of sleep per night for adults and possibly greater than 9 hours of sleep for adolescents or individuals recovering from sleep loss (Watson et al., 2015). It is troubling, then, that approximately one-third of U.S. adults reports fewer than 7 hours of sleep per night (Y. Liu, 2016). Sleep loss has been shown in both epidemiological and in-lab studies to result in suboptimal cognitive and affective functioning on a wide variety of neurobehavioral measures. The present work focuses on three domains in particular: appetitive desire, emotional face discrimination, and incentive-modulated inhibitory control.

## Sleep Loss & Appetite

**Increased caloric intake.** Several meta-analyses have found cross-sectional associations between markers of obesity and suboptimal sleep characteristics, including short sleep duration (Cappuccio et al., 2008; X. Chen, Beydoun, & Wang, 2008; Sperry, Scully, Gramzow, & Jorgensen, 2015) and insomnia symptoms (Chan, Levsen, & McCrae, 2018). Possibly contributing to these associations, an increase in caloric intake has been shown to follow sleep loss in the lab (Capers, Fobian, Kaiser, Borah, & Allison, 2015). For example, one study found that sleep restriction to 5.5 h time in bed (TIB) per night for 13 nights significantly increased participants' caloric intake from snacks, changing from 866 ± 365 (Mean ± SD) kcal/day of snacks in a well-rested condition (8.5 h TIB per night for 13 nights) to 1,087 ± 541 kcal/day of snacks when

sleep-restricted (Nedeltcheva et al., 2008). Another study restricted participants' sleep to 4 h TIB for 5 nights and found that, despite no change in the participants' resting metabolic rates or total energy expenditure, their calorie consumption increased. Specifically, it increased from 2,517.7 ± 593.0 kcal on the final day of a habitual sleep condition to 2,813.6 ± 593.0 kcal on the final day of the sleep-restricted condition (St-Onge et al., 2011). Notably, the increase in calorie consumption following experimentally induced sleep restriction has been reported to exceed the energy needed to offset the additional time spent awake, leading to a 0.82 ± 0.47 kg weight gain after 5 nights of 5 h TIB per night (Markwald et al., 2013). In the absence of a compensatory increase in energy expenditure, these findings support a plausible mechanism for excess weight gain with chronic sleep loss.

**Calorie-dense bias.** In addition to a sleep loss-related increase in caloric intake, sleep loss has been shown to induce a stronger preference for calorie-dense food choices. For example, one landmark study found that the effect of sleep restriction on appetite varied depending on the category of food on offer (Spiegel, Tasali, Penev, & Van Cauter, 2004). The effect on appetite was most pronounced for sweet, salty, and starchy food choices (33-45% increase), much less pronounced for fruits and vegetables (17-21% increase), and negligible for protein-dense foods like meat or dairy. Other studies have similarly observed a cognitive bias for calorie-dense foods, particularly fats and carbohydrates, following sleep loss (Benedict et al., 2012; Greer, Goldstein, & Walker, 2013; Markwald et al., 2013; Nedeltcheva et al., 2008; St-Onge et al., 2011).

**Leptin and ghrelin.** Multiple explanations have been proffered to explain the observed changes in appetite following sleep loss. Of the physiologic changes induced by sleep deficiency, one particularly well-studied change is the effect of sleep on hormones linked to appetite. Specifically, sleep duration affects circulating levels of leptin and ghrelin, which have been linked to satiety (Jéquier, 2002) and hunger (Cummings, Frayo, Marmonier, Aubert, & Chapelot, 2004) respectively. Experiments involving intravenous administration of ghrelin have observed increased food intake by men and women directly in response to the hormone (Wren et al., 2001). Similarly, food consumption declined and physical activity improved when leptin was administered to three leptin-deficient adults (Licinio et al., 2004). In larger samples, leptin has also been shown to reduce food intake in rodent and primate animal models (Abelenda, Ledesma, Rial, & Puerta, 2003; Tang-Christensen, Havel, Jacobs, Larsen, & Cameron, 1999).

**Leptin and ghrelin: Associations with short sleep duration.** The landmark study by Spiegel et al. (2004), which characterized the effects of sleep restriction on appetite under conditions of continuous glucose infusion, also identified a sleep restriction-induced decrease in leptin and an increase in ghrelin as measured from circulating blood plasma. Crucially, that study also found that the changes in hormone concentrations were correlated with reported changes in self-reported appetite and hunger. A few epidemiological studies also hint at a possible role for leptin and ghrelin in sleep-related fluctuations in appetite. The Wisconsin Sleep Cohort Study found that, relative to 8 hours of sleep per night, obtaining 5 hours predicted a 15.5% decrease in leptin levels and a 14.9% increase in ghrelin levels (Taheri, Lin, Austin, Young, & Mignot, 2004). Similarly, the Québec Family Study found that differences in circulating

leptin levels accounted for differences in adiposity between participants sleeping 5-6 hours per night and those sleeping 7-8 hours per night (J. P. Chaput, Després, Bouchard, & Tremblay, 2007).

**Leptin and ghrelin: Mixed experimental results.** Experiments examining the associations between short sleep and leptin or ghrelin concentrations have yielded mixed results. Consistent with Spiegel et al. (2004), some experiments have reported increased plasma concentrations of ghrelin or decreased plasma concentrations of leptin following sleep loss, without the continuous glucose infusion reported by Spiegel et al. (Buxton et al., 2012; J. P. Chaput et al., 2007; Rihm et al., 2019; Schmid, Hallschmid, Jauch-Chara, Born, & Schultes, 2008). On the other hand, several experiments have failed to replicate these hormonal changes (Bosy-Westphal et al., 2008; Nedeltcheva et al., 2008; Schmid et al., 2009), and several studies have actually documented an increase in leptin following sleep restriction (Bosy-Westphal et al., 2008; Omisade, Buxton, & Rusak, 2010; Pejovic et al., 2010; Simpson, Banks, & Dinges, 2010). Differences in study conditions that have been proposed to explain these divergent results include continuous glucose infusion without food intake on the day of the blood draws (Spiegel et al., 2004), continuous bed rest during blood draws (Nedeltcheva et al., 2008; Spiegel et al., 2004), and *ad libitum* food intake (Bosy-Westphal et al., 2008; J. P. Chaput et al., 2007; Simpson et al., 2010).

**Hedonic valuation.** Others have proposed that the appetitive changes following sleep loss may be explained by alterations in brain function affecting the hedonic valuation of food stimuli, rather than alterations in hormones affecting satiety (J.-P. Chaput & St-Onge, 2014; Nedeltcheva et al., 2008; Rihm et al., 2019). Exploring this

hypothesis using functional magnetic resonance imaging (fMRI), Benedict et al. (2012) reported that one night of total sleep deprivation, compared to a night with 7 hours TIB, resulted in greater activation of the right anterior cingulate cortex in response to food images. The change in activation between the two conditions was associated with the change in participants' self-reported appetite. Independently, St-Onge et al. (2012) exposed participants to a sleep restriction condition of 4 hours TIB for 5 nights and a rested condition of 9 hours TIB for 5 nights as part of an inpatient crossover study. Following the 5 nights of sleep restriction, they observed that brain regions that differentially responded to food images more than non-food images exhibited a global increase in activation, compared to the rested condition, when viewing the food images. Specifically, these brain regions included the insula, nucleus accumbens, orbitofrontal cortex, putamen, and thalamus.

**Hedonic valuation: Reward-related brain mechanisms.** Despite the lack of overlapping brain regions implicated in their studies, both groups of researchers argued for similar conclusions. Benedict et al. (2012) hypothesized that, due to its reciprocal connections with the striatum (Haber & Knutson, 2010), increased responsiveness of the anterior cingulate may reflect an increase in reward responsiveness. In addition, the authors noted that a similar increase in anterior cingulate responsiveness to food images had previously been observed in obese relative to healthy-weight adults (Martin et al., 2010), suggesting an analogy between sleep-deprived brain function and obese brain function. Given that half of their identified brain regions are well-known for their roles in the brain's reward network (Knutson & Cooper, 2005), St-Onge et al. similarly hypothesized that sleep restriction heightens participants' responsiveness to food

reward (St-Onge, Wolfe, Sy, Shechter, & Hirsch, 2014), while the insula and orbitofrontal cortex may reflect changes in the processing of interoceptive hunger signals (Tataranni et al., 1999) and complex behaviors associated with food seeking (DelParigi et al., 2007) respectively.

**Hedonic valuation: Resting-state connectivity.** Resting-state fMRI further elucidates how sleep loss may affect hedonic food valuation. Specifically, Fang et al. (2015) have argued that sleep restriction may be positively modulating connections in the brain's salience network. For instance, many of the brain regions identified in previous studies, particularly the anterior insula and the anterior cingulate cortex, are thought to be nodes in precisely such a salience network (Seeley et al., 2007; Taylor, Seminowicz, & Davis, 2009). To test this idea, Fang et al. (2015) conducted resting-state fMRI scans on acutely sleep-deprived participants. Upon comparing the resting-state connectivity against that of a rested condition, they found an increase in connectivity in the dorsal anterior cingulate with both the putamen and anterior insula, all of which co-activated together. Furthermore, the calories consumed *ad libitum* by participants in their study were associated with the dorsal anterior cingulate's connectivity with the putamen and anterior insula. Notably, all three of these regions have been implicated in fMRI studies examining obese participants' responses to food images, suggesting some analogy between the brains of obese and sleep-restricted individuals (García-García et al., 2013). This is consistent with arguments previously put forward by Benedict et al. (2012), who drew the same analogy. Behaviorally, the sleep-deprived participants showed an increased appetite for fatty foods, reduced appetite for carbohydrates, and an increased appetite for calorie-dense foods, on average,

compared to the rested condition. Some have reported similar findings with respect to fats and carbohydrates (St-Onge et al., 2011), but others have actually reported an increase in desire for carbohydrate-rich foods (Greer et al., 2013; Spiegel et al., 2004).

**Hedonic valuation: Molecular mechanisms.** Molecular mechanisms may contribute to changes in hedonic valuation. For instance, 2-arachidonoylglycerol (2-AG) and related endocannabinoids are thought not only to inform the brain about one's homeostatic need for food but also affect the hedonic qualities of food stimuli (Di Marzo, Ligresti, & Cristino, 2009). When 2-AG levels were compared between rested (8.5 h TIB per night for 4 nights) participants and those restricted to 4.5 h TIB per night for 4 nights, circulating 2-AG was found to exhibit consistently greater levels throughout the 24-hour cycle, and its plasma concentrations correlated with reported hunger and appetite (Hanlon et al., 2016). Like ghrelin, 2-AG concentrations also peaked in conjunction with actual caloric intake (Hanlon et al., 2016). 2-AG's proposed role in the hedonic valuation of stimuli differentiates it from leptin and ghrelin, which are generally thought to affect hunger and satiety, and offers a molecular mechanism that might work in concert with the changes in brain function reported in fMRI studies (Benedict et al., 2012; Fang et al., 2015; Greer et al., 2013; St-Onge et al., 2014).

**Behavioral evaluations in the fMRI scanner.** Most fMRI studies of sleep loss and appetite have involved passive exposure to food images in the scanner, but some of the more recent studies have taken a more active approach. Like previous studies, Greer et al. (2013) asked acutely sleep-deprived participants to view food images in a fMRI scanner, but unlike previous studies, they also asked participants to evaluate the desirability of the food images while in the scanner. The blood oxygen level-dependent

(BOLD) activation patterns they extracted from regions of interest were modulated using a parametric regressor corresponding to the participants' desirability ratings for each food image, such that activation correlated with increasing food desire. When changes in this modulated BOLD signal were evaluated across all participants relative to a rested condition, acute sleep deprivation was shown to suppress activation in the lateral orbitofrontal, anterior insular, and anterior cingulate cortices, while amplifying activation in the amygdala (Greer et al., 2013). Crucially, these changes were proportional to subjective sleepiness but independent of subjective hunger, thus implicating sleep deficiency but not the slight offset in energy expenditure from additional time spent awake. The study also succeeded in replicating the bias toward calorie-dense foods that had been previously observed in the literature (Benedict et al., 2012; Markwald et al., 2013; Nedeltcheva et al., 2008; Spiegel et al., 2004; St-Onge et al., 2011).

**Evaluative brain mechanism.** In light of their findings, Greer et al. proposed that the bias toward calorie-dense foods may be due to a bi-directional shift in neural activity, whereby higher-order, evaluative brain regions play a diminished role in determining food preferences but the subcortical, salience-processing amygdala plays a much greater role. These higher-order, evaluative brain regions include the lateral orbitofrontal, anterior insular, and anterior cingulate cortices. Previous work has singled-out these three brain regions for their role in integrating sensory features such as taste and odor that are recalled from memory when perceiving the flavor of food stimuli (Small & Prescott, 2005). Two of the three cortical regions, namely the lateral orbitofrontal cortex and the anterior insula, exhibited greater BOLD signal when participants attempted to suppress their desire for unhealthy food images by recalling

the long-term consequences of eating such foods, as opposed to when they simply allowed themselves to experience desire for those foods (Hollmann et al., 2012). Together, these findings suggest the lateral orbitofrontal cortex, anterior insula, and anterior cingulate cortex may be involved in more evaluative or deliberative processes that determine one's food preferences. Greer et al.'s proposed role for the amygdala also has some basis in prior literature. A meta-analysis by Van Der Laan, De Ridder, Viergever, and Smeets (2011) found that, when viewing images of food, activation in the amygdala was positively modulated by hunger. Because hunger promotes the biological salience (i.e., caloric content) of food stimuli, Van Der Laan et al. attributed their finding to the amygdala's proposed role in processing stimulus-salience, which may be either aversive or rewarding (Baxter & Murray, 2002). Since Greer et al.'s 2013 study, Janak and Tye (2015) have argued that salience may actually be encoded in the amygdala itself. Specifically, they ascribe salience to a region of overlap between two populations of neurons that have been shown to contribute to emotional arousal in response to aversive and appetitive stimuli, respectively, across multiple sensory modalities (Shabel & Janak, 2009). If true, this would mean that sleep-deprived participants' evaluations of food images rely disproportionately on salience-encoded features such as caloric content in the amygdala, and they rely much less on more deliberative processes in the cortex.

**Comparison with other studies.** In apparent contradiction with Greer et al.'s findings, other studies have observed increased BOLD signal in response to food images in the orbitofrontal cortex (St-Onge et al., 2012; St-Onge et al., 2014), insula (St-Onge et al., 2012), and anterior cingulate cortex (Benedict et al., 2012). However, none

of those studies instructed participants to evaluate the food items shown during fMRI. This is an important difference. For example, BOLD signal from the anterior cingulate can be either significantly increased or significantly decreased in obese participants versus healthy-weight participants depending on whether they are instructed to imagine the tastes of calorie-dense food images or merely to watch passively (Frankort et al., 2012). Therefore, it is possible that a similar effect might exist when contrasting sleep-restricted versus rested individuals.

**Ghrelin and evaluative brain mechanisms.** Most recently, a study by Rihm et al. (2019) also used fMRI to examine appetitive valuation following sleep deprivation. In a crossover study design, they conducted fMRI scans on participants following one night of habitual sleep at home and again following one night of total sleep deprivation in the lab. Prior to scanning, participants were given a small amount of money and asked to bid a portion of the money on a variety of food items and non-food trinkets. While in the fMRI scanner, participants were sequentially shown all of the same items, and for each item, they were asked whether they would, in order to have that item, be willing to pay the median price of all his or her bids placed prior to the scan. Similar to Greer et al. (2013), BOLD activation patterns were modulated by parametric regressors corresponding to pre-scan bids and on-task behavioral responses, such that activation correlated with subjective value. Compared to the rested condition, they found that BOLD signal in the hypothalamus, modulated by subjective value, was greater in the sleep-deprived condition. Separately, they also found that the amygdala, irrespective of subjective value, showed greater activation in the sleep-deprived condition specifically while viewing food images. Activation in the ventromedial prefrontal cortex (VMPFC),

irrespective of condition or stimulus type, correlated with subjective value. Furthermore, Rihm et al. (2019) also measured circulating ghrelin levels, but they failed to find any associations between ghrelin and functional activation. This led them to speculate that functional activation of brain regions associated with hedonic evaluation, but not circulating levels of hormones associated with satiety, might best account for the effects of sleep loss on appetite.

## Sleep Loss, Emotion, & Face Perception

**Affect, emotion, and mood.** There is extensive literature on the relationship between sleep and affective brain function (Goldstein & Walker, 2014). *Affect* refers to the class of mental states displaying both valence and arousal-based content (Barrett, Mesquita, Ochsner, & Gross, 2007; Mendl, Burman, & Paul, 2010). Emotions and moods are two types of affective states. *Emotions* are affective states that have some relational or situational content, such as how one feels toward another person or external stimulus (Barrett et al., 2007). Whereas emotions tend to be short-term and stimulus-evoked, *moods* correspond to the long-term momentum of affect, sometimes despite opposing, short-term fluctuations in emotion (Mendl et al., 2010). The influence of sleep on emotions is evident, for instance, in the finding that participants report positive stimuli to be more pleasant when sleep-deprived than when rested (Gujar, Yoo, Hu, & Walker, 2011). Similarly, it is widely thought that sleep loss tends to result in poorer mood the next day, an anecdotal view supported by controlled experiments (Baum et al., 2014; Beebe et al., 2008; Dinges et al., 1997; Tempesta et al., 2010).

**Consequences of sleep loss for affective functioning.** The repercussions of sleep loss for affective functioning extend well beyond fluctuations in mood. Couples are

more likely to report interpersonal conflict following nights of poor sleep (Gordon & Chen, 2014), suggesting a range of possible interpersonal consequences. In a hospital environment, physicians report greater emotional setbacks on the Positive Affect and Negative Affect Scales (PANAS) immediately following disruptive events (e.g., diverting time from medical duties to perform administrative duties) and report less of an emotional boost immediately following goal-enhancing events (e.g., encountering a medically interesting question) if they are not as well-rested as their colleagues (Zohar, Tzischinsky, Epstein, & Lavie, 2005). Even in response to relatively mild stressors, sleep-deprived individuals report greater stress, anger, and anxiety than rested controls (Minkel et al., 2012).

**Affective functioning and emotional face perception.** One aspect of affective functioning particularly sensitive to sleep loss is the perception of affect in other people's faces. Inaccurate perception of faces could have immediate interpersonal consequences. However, because the perception of facial affect informs impressions of not only temporary social cues but also stable psychological traits (Marsh, Adams Jr, & Kleck, 2005), the harm is not necessarily limited to the day immediately following sleep loss. For instance, traits inferred from facial stimuli have been shown to influence the outcomes of congressional elections (Todorov, Mandisodza, Goren, & Hall, 2005) and criminal sentencing (Zebrowitz & McDonald, 1991). The perception of affect in external facial expressions is contingent on many of the same affective processes involved in defining internal moods and emotions. For instance, it has been shown using facial electromyography that perceiving an emotional face causes the viewer unconsciously to mimic the same muscle movements as those seen in the facial cue (Dimberg,

Thunberg, & Elmehed, 2000), suggesting the autonomic signals entailed in such mimicry may play a role in interpreting affect in others (Critchley et al., 2005). Moreover, it has been shown that the perception of emotional faces is associated with subsequent increases in heart rate (Critchley et al., 2005), and these increases in heart rate subsequently influence the perception of affect in facial expressions (Goldstein-Piekarski, Greer, Saletin, & Walker, 2015; Gray et al., 2012).

**Face perception: Recognizing emotional faces.** Sleep deficiency and poor sleep quality have been repeatedly shown to impair the recognition of affect in others' faces. First, in 2004, a counterbalanced crossover study of male students in a Norwegian Naval Academy followed participants in a 5-day military training exercise, during which participants reported a mean of 4.25 h of sleep across all 5 days (Pallesen et al., 2004). Compared to those same participants after 12 h TIB for one night, the study found that sleep-restricted participants were slower and less accurate at recalling simple cartoon drawings of emotional facial expressions. Adding to these initial findings, Soffer-Dudek, Sadeh, Dahl, and Rosenblat-Stein (2011) gave children a "balloons task" in which they were instructed to pop floating balloons containing photographs of either a specified gender or a specified emotion. Simultaneously tracking the children's self-reported and actigraphic sleep, Soffer-Dudek et al. (2011) found that longitudinal performance on emotional face recognition, but not on gendered face recognition, was negatively associated with sleep inefficiency and with the number of nighttime awakenings across ages 10, 11, and 12.

**Face perception: Categorizing discrete emotions.** More recent work has tried to differentiate the effects of sleep according to the specific emotions displayed. For

instance, Maccari et al. (2014) collected separate photos of positive, negative, and neutral facial expressions, as well as positive, negative, and neutral sets of words. Compared to a rested baseline, they found that acutely sleep-deprived participants were less accurate at categorizing the valences of words regardless of which words were shown. However, participants' performances on the facial stimuli varied depending on whether the facial emotion was positive, negative, or neutral. Specifically, sleep-deprived participants showed the greatest effect in terms of both accuracy and reaction time on neutral faces, and they were slower and less accurate on negative and positive faces, respectively. In a similar vein, Holding et al. (2017) found that shorter self-reported sleep duration was associated with diminished accuracy at categorizing video footage of "disgusted" emotional displays but not any of the other 11 emotional displays they tested. However, the authors report that no such effect was observed for "disgusted" or for any other emotional display when they further tested this effect with an in-lab total sleep deprivation experiment (Holding et al., 2017). Taking a more clinical perspective, a study by Crönlein, Langguth, Eichhammer, and Busch (2016) examined insomnia and sleep apnea patients and tested the accuracy with which they categorized emotional faces. Relative to healthy participants, the insomnia and sleep apnea patients more often mischaracterized happy and sad faces. Zhang, Chan, Lau, and Hsiao (2018) also studied a clinical sample of insomnia patients. In addition to testing the accuracy with which participants categorized emotional faces, they tracked the participants' eye movements while observing the faces. Compared to age- and gender-matched controls, Zhang et al. (2018) found that the insomnia patients spent more time gazing at midline facial features and were more likely to mischaracterize angry faces as sad faces. These

results are consistent with previous eye-tracking studies which have found that attention to the mouth, a midline feature, is primarily responsible for accurate recognition of most facial expressions (Schyns, Petro, & Smith, 2009), whereas accurate recognition of angry facial expressions primarily depends on attention to the eyes, a more lateral feature (Eisenbarth & Alpers, 2011; Smith, Cottrell, Gosselin, & Schyns, 2005).

**Face perception: Categorizing ambiguous emotions.** Some research suggests that the effect of sleep loss on the categorization of emotions is easier to detect as the difficulty or ambiguity of the task increases (Huck, Mcbride, Kendall, Grugle, & Killgore, 2008; Killgore, Balkin, Yarnell, & Capaldi II, 2017). Specifically, researchers morphed together pairs of photographed faces conveying different emotions (e.g., happiness and anger) with varying contributions (e.g., 30% happiness and 70% anger) of each emotion (see Killgore et al., 2017 for examples). When they tested participants during a rested baseline and again following 47 h of total sleep deprivation, the researchers observed no effect on participants' accuracy when categorizing simple (e.g., merely happy) emotional faces, but they did observe a significant effect on participants' accuracy when discriminating the components of mixed (e.g., 30% happy and 70% angry) emotional faces (Huck et al., 2008). In a subsequent analysis, the researchers also found that the greatest effect existed for mixed faces in which happiness or sadness were the dominant emotions (Killgore et al., 2017). From an evolutionary perspective, the researchers argued this may reflect an adaptation for preserving the cognitive resources necessary to discriminate threat-related cues in angry or fearful faces, at the expense of discriminating affiliative cues in happy or sad faces (Killgore et al., 2017).

**Face perception: Varying emotional intensities in healthy participants.** In addition to differentiating the effects of suboptimal sleep on the categorization of specific emotions, several studies have further refined their analyses to specific emotional intensities. Van Der Helm, Gujar, and Walker (2010) randomized participants either to a sleep deprivation condition of 30 h of time spent awake, monitored overnight in the lab, or to a control condition of 8 h TIB at home. Each group was also given a second night of 12 or 8 h TIB, respectively, at home. After each night of the study, participants were asked to rate the emotional intensities of sad, angry, and happy faces that were digitally morphed to create 10-point spectra of emotional intensities for each of the three emotions. A within-subjects comparison found that only the acutely sleep-deprived group showed any change across the two time points. Specifically, sleep-deprived participants tended to underestimate the emotional intensities of happy and angry faces in the moderate-intensity range, which Van Der Helm et al. interpreted as emotionally "ambiguous" faces. Crucially, Van Der Helm et al. note that happy and angry faces are unique in their capacity to elicit reward- or threat-laden autonomic arousal, thus further bolstering a role for autonomic arousal in emotional face perception as reported in other studies (Critchley et al., 2005; Dimberg et al., 2000; Goldstein-Piekarski et al., 2015). Another experiment involving total sleep deprivation found that, compared to rested controls, sleep-deprived participants were slower to categorize all emotions but were less accurate specifically when categorizing sad faces, regardless of emotional intensity (Cote, Mondloch, Sergeeva, Taylor, & Semplonius, 2014). Although the observed behavioral effects did not vary with emotional intensity, the same study found that the N170 event-related potential, an electroencephalogram (EEG) signature commonly

associated with the perception of faces, increased in amplitude in proportion to the subtlety of angry and fearful faces. Consequently, the authors speculated that sleep loss may result in increased neural reactivity to threat-related stimuli (Cote et al., 2014). A subsequent at-home sleep restriction experiment similarly found that sleep loss affected participants' EEG recordings while categorizing emotional faces of varying intensities (Lustig et al., 2018). As in the previous study, they found that participants were less accurate when asked to categorize sad faces, and the N170 event-related potential increased in amplitude in response to sad faces, though they did not test the effect of specific emotional intensities on the EEG. Testing participants every 4 h over the course of 36 h of total sleep deprivation, Ginani, Pradella-Hallinan, and Pompéia (2017) observed a dose-dependent effect of sleep loss on how participants rated the emotional intensity of disgusted faces, whereby the perceived intensities of highly disgusted faces diminished with sleep loss. This effect was not seen for any other emotional faces, nor was the effect related to self-reported mood scales or to performance on a Psychomotor Vigilance Task (PVT).

**Face perception: Varying emotional intensities in clinical populations.** Complementing the literature on sleep deprivation in healthy sleepers, studies have also examined how clinical populations perform when discriminating faces of graded emotional intensities. Bayard, Croisier Langenier, and Dauvilliers (2013) tested emotional face discrimination separately among cataplectic narcolepsy patients, hypersomnia patients, and healthy sleepers. Participants were asked to rate the emotional intensity, pleasantness, and degree of arousal in each face from a set of emotional faces. Across all measures, the study found no differences in performance

between any of the three samples, suggesting narcolepsy with cataplexy may not have the same detrimental effects on emotional face perception as other suboptimal sleep characteristics (Bayard et al., 2013). However, a few studies have reported significant effects for insomnia patients, in addition to those previously described (Crönlein et al., 2016; Zhang et al., 2018). One such study found that, compared to healthy controls, insomnia patients tended to underrate the emotional intensities of faces, especially sad and fearful faces, but no effect was observed for the accuracy with which they categorized emotional faces (Kyle, Beattie, Spiegelhalder, Rogers, & Espie, 2014). Another study reported that, when emotionally neutral faces were digitally morphed to appear "tired" to varying degrees, insomnia patients were inclined to underrate the tiredness of morphed faces, compared to ratings provided by normal sleepers (Akram, Sharman, & Newman, 2018).

**Face perception: fMRI studies.** Despite the burgeoning literature on sleep and emotional face perception, only two studies have previously used fMRI to examine the underlying changes in brain function accompanying this phenomenon. First, a counterbalanced crossover study by Motomura et al. (2013) followed a sample of 14 male participants aged 20 to 32. As part of a sleep restriction condition, participants were allowed no more than 4 h TIB at home for 3 nights as verified by wrist actigraphy, and then, they were brought into the lab for another 2 nights of 4 h TIB while they underwent fMRI scans. As for the rested control condition, participants were required to spend 8 h TIB at home for 3 nights and were then brought into the lab for another 2 nights of 8 h TIB. After the 5th night of each condition, participants passively viewed photographs of faces digitally morphed to depict happy, fearful, or neutral emotions

while in the fMRI scanner. In addition, the emotional faces were either shown for 200 ms to guarantee conscious awareness of them, or they were shown for a subliminal duration of 26 ms, quickly masked by a neutral face for 174 ms. Compared to the rested condition, sleep-restricted participants exhibited increased BOLD activation in the left amygdala, the researchers' only hypothesized region of interest (ROI), in response to fearful faces. Moreover, Motomura et al. (2013) also hypothesized, based on previous research (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), that the amygdala would exhibit decreased functional connectivity with an area spanning the medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC). They found that connectivity between the amygdala and ventral ACC was negatively correlated with activation of the left amygdala, self-reported mood, and sleep debt as measured by the percentage of slow-wave sleep and delta-wave power from overnight polysomnography (PSG) data.

More recently, Goldstein-Piekarski et al. (2015) showed participants computer-generated faces that were morphed to depict varying degrees of threatening facial cues. In this case, "threatening" does not refer to the emotion embodied in an external face; "threatening" does not even describe an affective state. Rather, it is the participant's internal experience of feeling threatened that makes a threatening face threatening. Therefore, a participant's perception of threatening faces depends not only on the accurate perception of affect (e.g., anger) in external faces but also on his or her capacity to emote appropriately in response. For this reason, Goldstein-Piekarski et al. (2015) were not only interested in changes in brain function observable via fMRI but were also interested in peripheral autonomic activity, as measured by heart rate, associated with the participants' own emotions. In a counterbalanced crossover study,

Goldstein-Piekarski et al. (2015) demonstrated a diminished ability to discriminate between threatening and non-threatening faces following one night of total sleep deprivation, with a bias towards evaluating the faces as more threatening, relative to evaluations following a rested condition of approximately 8 h TIB. This behavioral deficit corresponded with the researchers' finding that viscerosensory brain regions, namely the anterior insula and dorsal ACC, failed to modulate their BOLD signal across threatening and non-threatening stimuli following sleep deprivation as they had in the rested condition. More specifically, the researchers found that BOLD signal from the anterior insula no longer increased in response to threatening faces any more than non-threatening faces. Meanwhile, the dorsal ACC exhibited the same increase in BOLD signal in response to non-threatening faces that, in a rested condition, was normally reserved only for threatening faces. Moreover, these changes directly corresponded with a behavioral deficit in participants' ability to discriminate threatening faces from non-threatening faces. Goldstein-Piekarski et al. also observed that activity in these viscerosensory brain regions was associated with concomitant increases in heart rate during the rested condition, but the association was not present in the sleep-deprived condition. They argued, therefore, that part of the mechanism underlying this bias toward threatening appraisals may be a decoupling of central and affect-related, peripheral nervous system activity.

### Sleep Loss & Incentive-Modulated Inhibitory Control

**Epidemiological relationship between sleep and risk-taking in adults.** A growing literature supports the view that sleep deficiency predisposes individuals to greater risk-taking behavior. For instance, one cross-sectional analysis of a nationally

representative sample of 9,282 U.S. participants found that, compared to participants with no gambling pathology, pathological gamblers were significantly more likely to report difficulty initiating sleep, difficulty maintaining sleep, early morning awakenings, or all three, after adjusting for age and psychiatric disorders (Parhami, Siani, Rosenthal, & Fong, 2013). Another cross-sectional analysis found that, when comparing a sample of 434 psychiatric patients who had attempted suicide against a sample of 83 psychiatric patients who had not, males who had attempted suicide were significantly more likely to report 5 or fewer hours of sleep on a typical night than males who had not attempted suicide (Blasco-Fontecilla et al., 2011). In females who had attempted suicide, the same study found that reporting 5 or fewer hours of sleep on a typical night was associated with measures of suicide risk and suicidal intent. There is also an established literature on the relationships between suboptimal sleep and substance use. One early study found that a sample of 533 patients with insomnia and no concurrent psychiatric disorders were, when compared to a sample of 6,172 healthy controls, at significantly greater risk for the onset of alcohol abuse one year later (Weissman, Greenwald, Niño-Murcia, & Dement, 1997). More recently, nationally representative data (n = 158,867) from the National Health Interview Survey found that adults in the period from 2004-2006 who reported sleeping 6 h or less on a typical night were more likely to report currently using cigarettes or to report 5 or more alcoholic drinks in a single day than respondents who reported any greater amount of sleep (Schoenborn & Adams, 2008). Similarly, health risk behaviors such as frequency of cigarette use, frequency of alcohol use, seriously considering suicide in the past 12 months, and having a physical fight in

the past 12 months were all associated with sleep complaints on the Sleep Quality Index in a sample of 859 undergraduates (Vail-Smith, Felts, & Becker, 2009).

**Epidemiological relationship between sleep and risk-taking in adolescents.** Although there have been numerous survey studies of the relationship between sleep and risk-taking in adults, the literature on adolescents is comparatively much more prolific. Alcohol use in adolescents has been associated with a variety of suboptimal sleep characteristics in both cross-sectional (Daly et al., 2015; Johnson & Breslau, 2001; McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Pasch, Laska, Lytle, & Moe, 2010; Reichenberger, Hilmert, Irish, Secor-Turner, & Randall, 2016; Terry-McElrath, Maslowsky, O'Malley, Schulenberg, & Johnston, 2016; Weaver, Barger, Malone, Anderson, & Klerman, 2018; Yen, King, & Tang, 2010) and longitudinal (Hasler, Martin, Wood, Rosario, & Clark, 2014; Haynie et al., 2017; McGlinchey & Harvey, 2015; Pieters et al., 2015; Wong, Brower, Fitzgerald, & Zucker, 2004; Wong, Robertson, & Dyson, 2015) analyses. Similar evidence links suboptimal sleep characteristics with adolescent use of tobacco products (Daly et al., 2015; Johnson & Breslau, 2001; McGlinchey & Harvey, 2015; McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Pasch et al., 2010; Pieters et al., 2015; Reichenberger et al., 2016; Terry-McElrath et al., 2016; Weaver et al., 2018; Wong et al., 2004). Other studies of adolescents have found significant relationships between suboptimal sleep characteristics and marijuana use (Daly et al., 2015; McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Pasch et al., 2010; Pieters et al., 2015; Reichenberger et al., 2016; Terry-McElrath et al., 2016; Weaver et al., 2018; Wong et al., 2004), as well as illicit drug use more broadly (Bagley, 2011; Johnson & Breslau, 2001; McGlinchey & Harvey, 2015; O'Brien & Mindell, 2005; Terry-McElrath et

al., 2016; Weaver et al., 2018; Wong et al., 2004; Wong et al., 2015; Yen et al., 2010). Apart from substance use, suboptimal sleep characteristics have been associated with various measures of adolescent suicidality (Daly et al., 2015; X. Liu, 2004; McGlinchey & Harvey, 2015; McKnight-Eily et al., 2011; Weaver et al., 2018; Wong, Brower, & Craun, 2016; Wong, Brower, & Zucker, 2011; Yen et al., 2010). The relationship with suicidality is particularly strong, with one study of 67,615 adolescents noting that suicidality had the strongest dose-dependent relationship with shorter sleep duration out of the eight disparate areas of risk-taking behavior that were assessed (Weaver et al., 2018). Notably, one longitudinal study found that sleep complaints at ages 12-14 predicted suicidal thoughts and self-harm behavior at ages 15-17 even after controlling for prior suicidal thoughts and self-harm behavior, as well as several other confounding variables (Wong et al., 2011). Many other risk-taking behaviors have similarly been associated with suboptimal sleep characteristics in adolescent survey studies. Briefly, some of these include dangerous driving behaviors (Weaver et al., 2018; Wong et al., 2015), theft or illegal destruction of property (Clinkinbeard, Simi, Evans, & Anderson, 2011; McGlinchey & Harvey, 2015; Yen et al., 2010), physical violence (Clinkinbeard et al., 2011; McGlinchey & Harvey, 2015; McKnight-Eily et al., 2011; O'Brien & Mindell, 2005; Weaver et al., 2018; Yen et al., 2010), truancy (Pasch et al., 2010; Yen et al., 2010), and measures of risky sexual behavior such as reporting having had sex without a condom or reporting alcohol-related sexual regret (O'Brien & Mindell, 2005; Weaver et al., 2018; Wong et al., 2015; Yen et al., 2010).

**Increased risk-taking on decision-making tasks: Iowa Gambling Task (IGT).** In addition to evidence from the epidemiological literature, further evidence of a link

between risk-taking behavior and suboptimal sleep comes from decision-making tasks administered in the lab. One such decision-making task is the IGT (Bechara, Damasio, Damasio, & Anderson, 1994). On the IGT, participants are instructed to draw from computerized decks of cards. Drawing certain cards will result in a gain of monetary reward, while other cards will result in a loss of monetary reward. Certain decks are more likely to produce a net gain, and certain decks are more likely to produce a net loss. However, the decks that produce a net loss also contain the highest valued cards. Over the course of the task, participants gradually learn which decks produce which kinds of cards. Participants are instructed to maximize monetary reward, given a limited number of draws. Risk-taking on this task is usually operationalized as the number of draws from high-risk decks, especially draws from the latter half of the task when participants are most likely to understand the risks associated with each deck. Killgore et al. have repeatedly shown that participants take more risks on the IGT after >48 h of total sleep deprivation, compared to when those same participants are well-rested (Killgore, Balkin, & Wesensten, 2006; Killgore, Grugle, & Balkin, 2012; Killgore, Lipizzi, Kamimori, & Balkin, 2007).

**Increased risk-taking on decision-making tasks: Lottery Choice Task (LCT).** Another kind of gambling task is the LCT (Ellsberg, 1961). On each trial of the LCT, participants are instructed to choose between two possible “gambles,” each with different odds of winning or losing money. In contrast with the IGT, trial-by-trial gambles vary in terms of whether they are framed in terms of gains versus losses, and they vary in terms of whether the precise odds of winning are known for both gambles versus only one of the two gambles. Each trial is designed such that one gamble involves greater

risk but also greater maximum payout than the other. In a randomized controlled experiment, participants completed the LCT after either receiving a restful night of sleep at home or being totally deprived of sleep for a single night in the lab. Compared to the rested control group, sleep-deprived participants took more gain-framed risks and fewer loss-framed risks on known-risk trials, but no effect was observed for ambiguous-risk trials (Mckenna, Dickinson, Orff, & Drummond, 2007). These results are consistent with those seen on the gain-framed IGT, and they introduce the possibility that individuals might actually become risk-averse following sleep loss if the risks are framed in terms of losses.

**Increased risk-taking on decision-making tasks: Balloon Analog Risk Task (BART).** Like the IGT and LCT, the BART is another decision-making task used to assess risk-taking propensity. On the BART, participants are given the opportunity to win money in exchange for virtual balloons. At the outset of the task, participants are allotted a predetermined number of balloons, and for each balloon, participants have the option either to collect the balloon for its associated monetary value or to inflate the balloon, thereby increasing the balloon's associated monetary value. Participants may inflate each balloon as many times as they wish, but each inflation of a balloon increases the odds that it will burst, reducing its associated monetary value to zero. Participants are instructed to try to maximize their monetary reward. Rossa, Smith, Allan, and Sullivan (2014) brought participants into the lab and gave them a BART with 90 virtual balloons as part of a within-subjects, at-home sleep restriction study that monitored participants' sleep using wrist actigraphy devices. In a counterbalanced crossover design, participants were allowed either one full night of habitual sleep for an

average of 6.7 h or one night of restricted sleep for an average of 3 h before being awoken by a phone call. On multiple measures (cost-benefit ratio and number of burst balloons), participants exhibited greater risk-taking on the BART following the night of sleep restriction versus the night of habitual sleep (Rossa et al., 2014). Notably, the same study also included a go/no-go task that showed no effect of sleep restriction. These two findings taken together suggest that inhibitory control might not, by itself, be sufficient to explain the relationship between suboptimal sleep and risk-taking. More recently, increased risk-taking (mean adjusted pumps) on the BART has been documented following one night of total sleep deprivation as well (Lei et al., 2017).

**Increased risk-taking on decision-making tasks without incentives.** Apart from tasks that offer performance-based monetary incentives, some studies have tried evaluating risk-taking via simulations of day-to-day activities that lack performance-based gains or losses. Rusnac, Spitzenstetter, and Tassi (2018) compared groups of participants with insomnia, habitual short sleep, or normal sleep on the Vienna Risk-Taking Traffic Test, a validated test of risk-taking in road traffic (Hergovich, Arendasy, Sommer, & Bognar, 2007). In brief, this computerized test shows participants video footage of realistic traffic situations in which the driver has an opportunity to initiate a driving maneuver (e.g., proceed from a stopped position at a crosswalk), and the participants are asked to indicate the moment during the video footage at which they would no longer feel comfortable making the relevant driving maneuver (e.g., a pedestrian has entered the crosswalk). Rusnac et al. (2018) found that only the habitual short sleepers, not the insomniacs, took more driving risks compared to the healthy controls, suggesting that certain suboptimal sleep characteristics are closer associated

with risk-taking than others. Furthermore, only the habitual short sleepers reported drinking more alcohol and being more disinhibited on the sensation seeking scale. Another study by Aran, Wasserteil, Gross, Mendlovic, and Pollak (2017) examined risk-taking in a sample of pediatric physicians after 3 nights of restful sleep versus after a 24-hour call with little sleep. Presented with binary choices in hypothetical medical scenarios with well-known guidelines, the physicians tended to make riskier medical decisions after the 24-hour call only if they napped <1 h while on call versus when they were rested. This means that emergency rooms might be susceptible to unnecessary risk-taking due to sleep loss, yet 1 h of additional sleep might be enough to forestall some of these effects (Aran et al., 2017).

**Decreased risk-taking on decision-making tasks.** As already mentioned, total sleep deprivation has been shown selectively to reduce risk-taking when the risks are framed in terms of losses (Mckenna et al., 2007). However, some studies have observed diminished risk-taking under conditions that are not as easily explained in terms of framing (Acheson, Richards, & de Wit, 2007; Chaumet et al., 2009; Killgore, 2007; Killgore et al., 2008; Killgore, Kamimori, & Balkin, 2011), while others have observed no change in risk-taking at all on certain tasks and in-lab questionnaires (Acheson et al., 2007; Bagley, 2011; Brown, 2008; Killgore et al., 2011; Schaffner, Sarkar, Torgler, & Dulleck, 2018). Although no single explanation can account for all of their findings, it is noteworthy that six out of these eight studies used the BART (Acheson et al., 2007; Bagley, 2011; Brown, 2008; Killgore, 2007; Killgore et al., 2008; Killgore et al., 2011). One reason why risk-taking on the BART might decrease or remain unaffected following sleep loss is that, in contrast with other risk-taking tasks like

the IGT or LCT, it requires greater effort in order to take greater risks on the BART. Whereas the IGT and LCT require the same number of key presses whether the participant wishes to make the riskier choice or the safer choice, the BART requires more key presses in order to take risks. Killgore (2015) suggests this may be an example of effort discounting, the well-known phenomenon whereby participants are biased against choices that involve greater effort. In support of this hypothesis, effort discounting has been shown in laboratory experiments to increase following total sleep deprivation (Libedinsky et al., 2013). Similarly, Killgore (2007) observes that most of the questions on the Evaluation of Risks (EVAR) scale ask participants to consider taking risks that would require additional energy expenditure. The EVAR scale was used in four out of the eight aforementioned studies that found decreased or unaffected risk-taking following sleep loss (Chaumet et al., 2009; Killgore, 2007; Killgore et al., 2008; Killgore et al., 2011). However, there may still be conditions under which sleep-deprived or sleep-restricted participants are willing to take more risks despite the additional effort. As previously mentioned, two studies have in fact reported increased risk-taking on the BART after a single night of sleep restriction to roughly 3 h TIB (Rossa et al., 2014) and after one night of total sleep deprivation (Lei et al., 2017). In addition, Killgore's own lab has shown that, although sleep deprivation of 23 h or more can reduce (Killgore, 2007; Killgore et al., 2008) or fail to affect risk-taking on the BART (Killgore et al., 2011), total sleep deprivation beyond a threshold of 75 h appears sufficient to increase risk-taking on the BART (Killgore et al., 2011). This may be due to accumulating dose-dependent changes in inhibitory control and reward processing, or it may simply be a means of self-stimulation to offset sleepiness (Killgore, 2015).

**Meta-analytic results and converging lines of evidence.** Although carefully conducted studies have identified a variety of circumstances under which this general relationship does not hold, literature reviews have consistently found a positive relationship between suboptimal sleep and increased risk-taking (Edwards, Reeves, & Fishbein, 2015; Harrison & Horne, 2000; Killgore, 2015; Short & Weber, 2018; Womack, Hook, Reyna, & Ramos, 2013). Most recently, a meta-analysis of 24 studies on adolescents calculated that insufficient sleep, defined and weighted differently according to individual studies, was associated with 1.43 (CI: 1.26-1.62) times greater odds of adolescents engaging in a variety of different risk-taking behaviors. Moreover, the hypothesized relationship holds true in the opposite direction as well; complementing the previously reviewed experiments that restrict participants' sleep, there is also evidence that risk-taking can be mitigated by improving sleep. Specifically, a mindfulness intervention for 55 adolescents in a substance abuse treatment program found that program completion was associated with increased sleep duration, and increased sleep duration was, in turn, associated with relapse resistance and fewer substance use-related problems at a 60-week follow-up (Britton et al., 2010).

**Neural correlates of risk-taking and reward with suboptimal sleep.** Several studies have used neuroimaging techniques to investigate the neurocognitive mechanisms underlying this relationship between suboptimal sleep and risk-taking. In one fMRI study, participants reporting poorer sleep quality on the Pittsburgh Sleep Quality Index (PSQI) showed greater activation in the left insula during trials when they won money on the BART (Telzer, Fuligni, Lieberman, & Galvan, 2013). Furthermore, the percent BOLD signal change in the left insula was associated with balloon pumps

(inflations) on the BART and greater likelihood of risk-taking as assessed by the Cognitive Appraisal of Risk Activities questionnaire. In addition, mediation analyses from the same study revealed that weaker recruitment of the dorsolateral prefrontal cortex (DLPFC) on a go/no-go task, which the researchers found was associated with poorer inhibitory control, mediated the percent signal change in the insula during BART payouts (Telzer et al., 2013). In a separate set of fMRI studies, sleep-deprived participants showed increased BOLD response in the nucleus accumbens and dorsal anterior cingulate cortex (DACC) during decision-making on a gambling task, relative to when rested (Venkatraman, Chuah, Huettel, & Chee, 2007). Moreover, a *post hoc* analysis found that the increased BOLD response in the nucleus accumbens was only observed for trials on which participants chose the riskier option (Venkatraman et al., 2007). Winning money, on the other hand, was associated with greater activation in the left orbitofrontal cortex (OFC), right superior frontal gyrus, and left anterior insula, only the latter of which was replicated when the researchers modified their original paradigm to better isolate reward processing (Venkatraman et al., 2007). In a subsequent fMRI study, the same team of researchers found that, consistent with previous findings (Mckenna et al., 2007), sleep-deprived participants tended to take more risks if the risks were framed in terms of gains but took fewer risks if the risks were framed in terms of losses (Venkatraman, Huettel, Chuah, Payne, & Chee, 2011). The researchers also observed that, during decision-making phases of a gambling task, sleep-deprived participants showed diminished activation in the VMPFC and bilateral intraparietal sulcus (IPS). Specifically during the decision-making phases of loss-framed trials, sleep-deprived participants showed reduced activity in the right anterior insula and

dorsomedial prefrontal cortex (DMPFC), and reductions in both of these regions correlated with behavioral changes. Finally, the researchers also observed increased activation in the left ventral striatum and VMPFC during payouts, and they saw decreased activation in the left anterior insula during losses, which correlated with the increased striatal activation during payouts (Venkatraman et al., 2011). In a separate study, participants who were given the opportunity to win money on a card-guessing game exhibited greater BOLD signal in the ventral striatum during reward blocks when they were sleep-deprived than when they were rested (Mullin et al., 2013). Moreover, while rested participants showed decreased activation in the MPFC during reward relative to neutral blocks on the card-guessing game, the same degree of deactivation was not seen following sleep deprivation (Mullin et al., 2013). Looking instead at differences in sleep timing, others have observed diminished activation in the MPFC (anterior cingulate and superior frontal gyrus) and bilateral striatum (caudate, putamen, and nucleus accumbens) during passive reward processing on the same card-guessing game in adolescents who had greater lag between weekday and weekend sleep midpoints (Hasler et al., 2012). Other neuroimaging work involving passive reward processing, such as being shown pleasantly rated images from the International Affective Picture System, has found increased reward-related reactivity in the ventral tegmental area (VTA), left putamen, bilateral amygdala, and left insula following total sleep deprivation (Gujar et al., 2011). Most recently, a counterbalanced crossover study by Lei et al. (2017) compared performance on a BART in a fMRI scanner following a restful night of habitual sleep at home versus one night of total sleep deprivation in the lab. Compared to the rested condition, sleep-deprived participants exhibited greater

activity in the left inferior frontal gyrus as a function of the number of balloon pumps per trial, and functional coupling between the posterior cingulate and VMPFC decreased with the number of balloon pumps. Moreover, these two findings were related such that increased activity in the left inferior frontal gyrus mediated the change in coupling between the posterior cingulate and VMPFC. During payouts, increased activation was seen in the ventral striatum and thalamus following sleep deprivation, and decreased activation was seen in the bilateral lingual gyrus (Lei et al., 2017).

**Antisaccade performance.** Scarcely found in the sleep literature, the antisaccade task offers a novel approach to studying inhibitory control and reward processing in sleep study participants. On the antisaccade task, participants are instructed to direct their gaze horizontally in the opposite direction (producing an "antisaccade") of stimuli that appear along the horizontal axis in either the left or right visual hemifield. Because of the visually salient nature of these stimuli, the antisaccade task is thought to require inhibitory control in order to resist the urge to look towards the stimulus (Munoz & Everling, 2004). Of particular relevance to the risk-taking literature, some versions of the task include trials on which performance can result in either a gain or loss of reward. To this author's knowledge, no sleep study has yet administered an antisaccade task with incentive-modulated trials, and no sleep study has yet administered an antisaccade task in tandem with fMRI. However, a handful of studies have tested antisaccade performance in otherwise healthy participants with various suboptimal sleep characteristics. Results have been mixed. Some studies have found increased error rates (Bocca, Marie, & Chavoix, 2014; Lee, Manousakis, Fielding, & Anderson, 2015; Meyhöfer, Kumari, Hill, Petrovsky, & Ettinger, 2017) and latencies

(Bocca et al., 2014; Fimm & Blankenheim, 2016) following sleep loss, while others have found neither (Crevits, Simons, & Wildenbeest, 2003; Zils, Sprenger, Heide, Born, & Gais, 2005). As others have suggested (Bocca et al., 2014; Lee et al., 2015), this discrepancy might be due to differences in the timing of procedures between the rested and sleep-deprived conditions. Whereas all the studies reporting an effect on the error rate have tested their participants at an internally consistent time of day (Bocca et al., 2014; Lee et al., 2015; Meyhöfer et al., 2017), all studies that have not found this effect have tested their participants in the evening during the rested condition and in the morning during the sleep-deprived condition (Crevits et al., 2003; Fimm & Blankenheim, 2016; Zils et al., 2005). This is potentially confounding because performance on oculomotor tasks by sleep-restricted participants has been shown to vary with time of day, such that directional errors peak in the afternoon and premature reactions constantly increase over the course of the day (Wachowicz et al., 2015).

**Incentive modulation.** When tests of inhibitory control have been paired with performance incentives, the addition of these incentives has been found to improve inhibitory control performance (Boehler, Hopf, Stoppel, & Krebs, 2012; Guitart-Masip et al., 2012), including on the antisaccade task (Duka & Lupp, 1997; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Hardin, Schroth, Pine, & Ernst, 2007; Jazbec et al., 2006; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Paulsen, Hallquist, Geier, & Luna, 2015). FMRI studies of incentive modulation on the antisaccade task reveal that numerous regions exhibit greater BOLD activity on reward relative to neutral trials. These regions include the right OFC (Padmanabhan et al., 2011), left medial frontal gyrus and/or ACC (Geier et al., 2010), right DLPFC (Paulsen et al., 2015), frontal eye

fields (FEFs; Geier et al., 2010; Paulsen et al., 2015), pre-supplementary motor area (pre-SMA; Paulsen et al., 2015), right inferior precentral sulcus (Geier et al., 2010), left superior precentral sulcus (Geier et al., 2010), right IPS (Padmanabhan et al., 2011), left inferior parietal lobule (IPL; Geier et al., 2010), right posterior parietal cortex (PPC; Paulsen et al., 2015), bilateral caudate (Paulsen et al., 2015), bilateral putamen (Padmanabhan et al., 2011; Paulsen et al., 2015), bilateral nucleus accumbens or ventral striatum (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015), and right amygdala (Paulsen et al., 2015). Notably, there are areas of overlap between the brain networks that are sensitive to incentive modulation on tests of inhibitory control (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015) and networks that are sensitive to pleasant or rewarding stimuli with suboptimal sleep (Gujar et al., 2011; Lei et al., 2017; Mullin et al., 2013; Telzer et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011). Namely, these are the putamen (Gujar et al., 2011; Padmanabhan et al., 2011; Paulsen et al., 2015), ventral striatum (Geier et al., 2010; Lei et al., 2017; Mullin et al., 2013; Padmanabhan et al., 2011; Paulsen et al., 2015; Venkatraman et al., 2007; Venkatraman et al., 2011), and amygdala (Gujar et al., 2011; Paulsen et al., 2015).

## Aims of the Present Study

### Aims

While past research has primarily focused on the effects of one night of total sleep deprivation, the present work examined the effects of 5 nights of sleep restriction to 5 h TIB. Specifically, the goal of this work was to extend past findings on appetitive evaluation and emotional face discrimination following one night of total sleep

deprivation to conditions more reflective of the typical work week. Furthermore, the present work also sought to test incentive-modulated inhibitory control performance and accompanying changes in brain function.

## Hypotheses

**Behavioral hypotheses.** It was hypothesized that the changes previously reported following one night of total sleep deprivation would extend to conditions of 5 nights of sleep restriction to 5 h TIB. Behaviorally, it was expected that participants would report a stronger preference for calorie-dense over calorie-sparse foods, as measured by a food desirability task in the fMRI scanner and by appetite questionnaires before every meal. A bias for calorie-dense foods has previously been reported following sleep loss in the lab (Benedict et al., 2012; Fang et al., 2015; Greer et al., 2013; Spiegel et al., 2004; St-Onge et al., 2011; St-Onge et al., 2014). On a social threat discrimination task, it was hypothesized that sleep-restricted participants would become more likely to judge faces as threatening, as has been previously reported following one night of total sleep deprivation (Goldstein-Piekarski et al., 2015). Consistent with most sleep restriction studies that have examined performance on the antisaccade task (Bocca et al., 2014; Lee et al., 2015; Meyhöfer et al., 2017), it was expected that accuracy would degrade on an incentive-modulated antisaccade task following sleep restriction, particularly on rewarded antisaccade trials. Although the antisaccade task already provided one measure of incentive-modulated inhibitory control, risk-taking was also investigated more directly on a BART, administered approximately every two hours of the study. Previous studies have reported both increases (Lei et al., 2017; Rossa et al., 2014) and decreases (Acheson et al., 2007;

Killgore, 2007; Killgore et al., 2008) in risk-taking on the BART following sleep loss, so it was difficult to predict what effect partial sleep restriction might have had on task performance. Nevertheless, performance on the BART was assessed because of the robust positive association between short sleep duration and risk-taking behaviors in previous literature (Edwards et al., 2015; Harrison & Horne, 2000; Killgore, 2015; Short & Weber, 2018; Womack et al., 2013). With regards to neuroimaging, the following sections outline hypotheses concerning changes in ROI activation following 4 nights of 5 h TIB versus a rested baseline sleep condition. ROIs are summarized in Table 1.

**Appetitive desire ROIs.** Following Greer et al. (2013), the contrast between baseline versus sleep restriction conditions on the food desirability task was expected to reveal diminished activation in the right anterior cingulate (x: 15, y: 6, z: 35), left anterior insula (x: -30, y: 19, z: 12), right anterior insula (x: 34, y: 14, z: 3), and left lateral OFC (x: -35, y: 37, z: -7) following sleep restriction, whereas the right amygdala (x: 17, y: -14, z: -15) was expected to show greater activation.

**Affective discrimination ROIs.** Following Goldstein-Piekarski et al. (2015), the left (x: -33, y: 14, z: -5) and right (x: 34, y: 16, z: -1) anterior insula were expected to show diminished BOLD signal in response to threatening stimuli in the sleep restriction condition relative to baseline. Simultaneously, the left DACC (x: -7, y: 25, z: 37) was expected to show greater BOLD signal in response to non-threatening stimuli following sleep restriction. Furthermore, it was expected that, in contrast with the rested baseline condition, no differences in BOLD signal would be observed on stimuli that the participants rated threatening versus those they rated non-threatening during the sleep

restriction condition. This would be consistent with results also reported by Goldstein-Piekarski et al. (2015).

**Incentive-modulated inhibitory control ROIs.** Following Padmanabhan et al. (2011), brain regions exhibiting a general effect of time-into-trial for correct antisaccade responses on the incentive-modulated antisaccade task were examined. Padmanabhan et al. (2011) also reported various interactions of incentive by age in six of these twelve regions, but because no study has yet examined brain function on this task following sleep restriction in young adults, the present study sought to identify possible effects of incentive by sleep condition across all these regions. Therefore, this approach is similar to the methodology reported in previous fMRI studies examining the effects of incentive on regional brain activation (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015), all of which focused on *a priori* regions known for their contributions to reward processing or oculomotor control on this task. Present ROIs, as defined by Padmanabhan et al. (2011), included the left FEF (x: -22, y: -8, z: 48), right FEF (x: 29, y: -11, z: 46), supplementary eye field (SEF; x: 2, y: -2, z: 52), left superior parietal lobule (SPL; x: -25, y: -59, z: 43), right SPL (x: 26, y: -62, z: 43), right IPS (x: 41, y: -44, z: 40), right DACC (x: 8, y: 7, z: 34), left putamen (x: -22, y: 4, z: 1), right putamen (x: 20, y: 7, z: 4), left ventral striatum (x: -10, y: 8, z: -4), right ventral striatum (x: 14, y: 8, z: -4), and right OFC (x: 35, y: 28, z: -11). Of these regions, it was specifically hypothesized that the putamen and ventral striatum would show greater activation on rewarded antisaccade trials during sleep restriction versus rewarded antisaccade trials when rested at baseline. This hypothesis was based on the observation that these regions had not only shown enhanced reward-related activity on the antisaccade task

(Padmanabhan et al., 2011; Paulsen et al., 2015) but also shown enhanced reward-related activity following total sleep deprivation (Gujar et al., 2011; Mullin et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011). Additionally, it was hypothesized that greater activation would be seen in the left (x: 29, y: 8, z: -15) and right (x: -15, y: 6, z: -8) amygdala on rewarded antisaccade trials during sleep restriction versus rewarded antisaccade trials at baseline. These latter two ROIs were derived from results reported by Paulsen et al. (2015). Following a paradigm similar to Padmanabhan et al. (2011), Paulsen et al. (2015) found increased reward-related activation in the amygdala on incentivized antisaccade trials. The amygdala's inclusion in these hypotheses was motivated by the observation that increased reward-related activity in the amygdala had also been seen by Gujar et al. (2011) following total sleep deprivation, making it a plausible ROI for the current study as well.

**Table 1. Brain Regions of Interest**

| | Region | X | Y | Z | Reference |
|---|---|---|---|---|---|
| Food Desirability Task | ACC (right) | 15 | 6 | 35 | Greer et al. (2013) |
| | Amygdala (right) | 17 | -14 | -15 | Greer et al. (2013) |
| | Anterior Insula (left) | -30 | 19 | 12 | Greer et al. (2013) |
| | Anterior Insula (right) | 34 | 14 | 3 | Greer et al. (2013) |
| | OFC (left) | -35 | 37 | -7 | Greer et al. (2013) |
| Social Threat Discrimination Task | Anterior Insula (left) | -33 | 14 | -5 | Goldstein-Piekarski et al. (2015) |
| | Anterior Insula (right) | 34 | 16 | -1 | Goldstein-Piekarski et al. (2015) |
| | DACC (left) | -7 | 25 | 37 | Goldstein-Piekarski et al. (2015) |
| Incentive-Modulated Antisaccade Task | Amygdala (left) | -29 | -8 | -15 | Paulsen et al. (2015) |
| | Amygdala (right) | 15 | -6 | -8 | Paulsen et al. (2015) |
| | DACC (right) | 8 | 7 | 34 | Padmanabhan et al. (2011) |
| | FEF (left) | -22 | -8 | 48 | Padmanabhan et al. (2011) |
| | FEF (right) | 29 | -11 | 46 | Padmanabhan et al. (2011) |
| | IPS (right) | 41 | -44 | 40 | Padmanabhan et al. (2011) |
| | OFC (right) | 35 | 28 | -11 | Padmanabhan et al. (2011) |
| | Putamen (left) | -22 | 4 | 1 | Padmanabhan et al. (2011) |
| | Putamen (right) | 20 | 7 | 4 | Padmanabhan et al. (2011) |
| | SEF | 2 | -2 | 52 | Padmanabhan et al. (2011) |
| | SPL (left) | -25 | -59 | 43 | Padmanabhan et al. (2011) |
| | SPL (right) | 26 | -62 | 43 | Padmanabhan et al. (2011) |
| | Ventral Striatum (left) | -10 | 8 | -4 | Padmanabhan et al. (2011) |
| | Ventral Striatum (right) | 14 | 8 | -4 | Padmanabhan et al. (2011) |

*Note.* X, Y, and Z coordinates correspond to neurological (LPI/SPM) coordinates in Talairach space. When necessary, these were converted from the Montreal Neurological Institute (MNI) space coordinates reported by some of the listed references. Conversions used the MNI to Talairach Coordinate Converter provided by the Yale School of Medicine's online BioImage Suite (http://bioimagesuite.yale.edu/mni2tal/).

# Chapter 2. Approach

## Overview

## Recruitment & Screening

Prospective participants for the study were recruited through ads on online forums (Pennsylvania State University research websites and https://pennstate.craigslist.org/) and bulletin boards across the Pennsylvania State University Park campus and surrounding State College area. To be considered for the study, applicants needed to meet several criteria. First, because this study was not interested in questions about adolescent development or healthy aging, the range of acceptable applicants for this study was constrained to those aged 20-35 years. Second, to ensure the safety of participants in the fMRI environment and the validity of fMRI results, this study required that applicants have no metallic implants, history of serious head trauma, claustrophobia, or color blindness. Left-handed participants were also excluded to avoid motor lateralization effects in the fMRI data. Third, to avoid health confounds, applicants could not have any acute or chronic medical condition. Similarly, since this study was only interested in healthy normal sleepers, applicants could not have any history of sleep or chronobiologic disorders, inability to maintain a regular sleep schedule, history of nighttime work in the preceding 3 years, or history of traversing more than 2 time zones in the preceding 3 months. Moreover, to ensure they were rested insofar as possible and that they were suited for an in-lab sleep study, applicants needed to comply with at-home sleep monitoring procedures (lying in bed and trying to sleep 10 hours each night for 7 nights) preceding the inpatient portion of

the study. Finally, due to the intensive nature of this study, applicants also needed to pass a structured clinical exam by a psychologist in order to ensure they possessed the mental capacity and emotional resilience to complete the 11-day inpatient protocol. All participants provided written informed consent and were paid for their participation in the study.

The current sample only included male participants. Since each inpatient portion of the study spanned 11 days, fluctuations in the ovulatory cycle could have confounded a variety of subjective and objective measures of sleep (Baker & Lee, 2018), in addition to possible confounding effects for the cognitive and behavioral domains of central interest to this study (Gorczyca et al., 2016; Iannello, Biassoni, Nelli, Zugno, & Colombo, 2015; Yamazaki & Tamura, 2017). Due to the pilot nature of the study, it was not feasible to enroll an equal number of female participants to match the enrolled male participants while also controlling for these confounds. The implications of this design limitation are discussed in the Discussion chapter.

**Sleep Study Protocol**

This 11-day inpatient study followed a within-subjects design, exposing each participant to all three of the following conditions: rested baseline, sleep restriction, and sleep recovery (Figure 1). The rested baseline condition consisted of 3 nights of 10 h TIB. To ensure, insofar as possible, that participants were truly sleep-replete in the baseline sleep condition, participants underwent outpatient monitoring for 7 days immediately prior to admission into the study. For those 7 days, participants were instructed to go to bed at the same time each night and to spend 10 h in bed trying to sleep. Following the rested baseline condition, participants were confined to 5 h TIB for

5 nights comprising the sleep restriction condition. Restriction to 5 h or fewer in bed per night has been shown to worsen fatigue and induce cumulative decrements in attention for at least a full week (Belenky et al., 2003; Dinges et al., 1997; Van Dongen, Maislin, Mullington, & Dinges, 2003), with significant differences even after only two nights (Dinges et al., 1997). The final 2 nights of the study consisted of 10 h TIB for sleep recovery.

Preceding the final night of each condition, participants underwent fMRI scans at 14:30 in the afternoon. During each fMRI scan, participants were given three neurobehavioral tasks: a food desirability task, a social threat discrimination task, and an incentive-modulated antisaccade task. In addition, participants completed a Balloon Analog Risk Task (BART) approximately every two hours of scheduled wake time throughout the study (Figure 1). Participants were also instructed to complete appetite questionnaires before and after each meal of the study.

A controlled nutrient diet using weighed foods with predetermined macronutrient and micronutrient content (58-60% carbohydrate, 15-17% protein, 25-27% fat, 800-1000 mg Ca/day, 100 mEq K, and 200 mEq Na) was provided to all participants throughout the in-lab study conditions. Food volumes were adjusted to offset each participant's daily caloric expenditure as determined by an average of the Harris-Benedict and Mifflin-St. Jeor equations, with activity factors of 1.1 and 1.5 respectively (Frankenfield, Roth-Yousey, Compher, & Group, 2005; Harris & Benedict, 1918). Participants were instructed to consume all food provided, and participants' weights were monitored daily to ensure stability.

This study design was approved by the Pennsylvania State University's Institutional Review Board.

**Laboratory Conditions**

Participants were housed in a private room at Pennsylvania State University's Clinical Research Center (CRC) for all 11 days of the inpatient study. Light levels were controlled with semi-transparent light covers, window padding, and black strips around the edges of the door. During scheduled sleep periods, participants were kept in complete darkness (0 lux), and once per day during scheduled wake periods, light levels in the room were recorded and kept below 100 lux in the angle of gaze. In order to minimize the circadian-disrupting effects of blue light exposure, participants were not allowed access to light-emitting devices (e.g., cellphones, laptops) during scheduled sleep periods nor during the two hours before or the two hours after scheduled sleep periods. To ensure wakefulness during scheduled wake periods, participants were continuously monitored by study staff at the CRC during scheduled wake periods. Except during scheduled sleep periods, participants were required to sit or to stand upright at all times and were not allowed to sit on the bed. Exercise was limited to light stretching.

**Participants**

A total of 15 males completed the study. Although 17 participants were enrolled in the study, two participants voluntarily withdrew before completing the study, leaving a final sample of 15 participants. The final sample was 60% White and non-Hispanic. Their ages ranged from 19 to 29 years (Mean ± SD: 22.33 ± 2.82 years), and their mean body mass index (BMI) was 24.69 ± 2.99 $kg/m^2$.

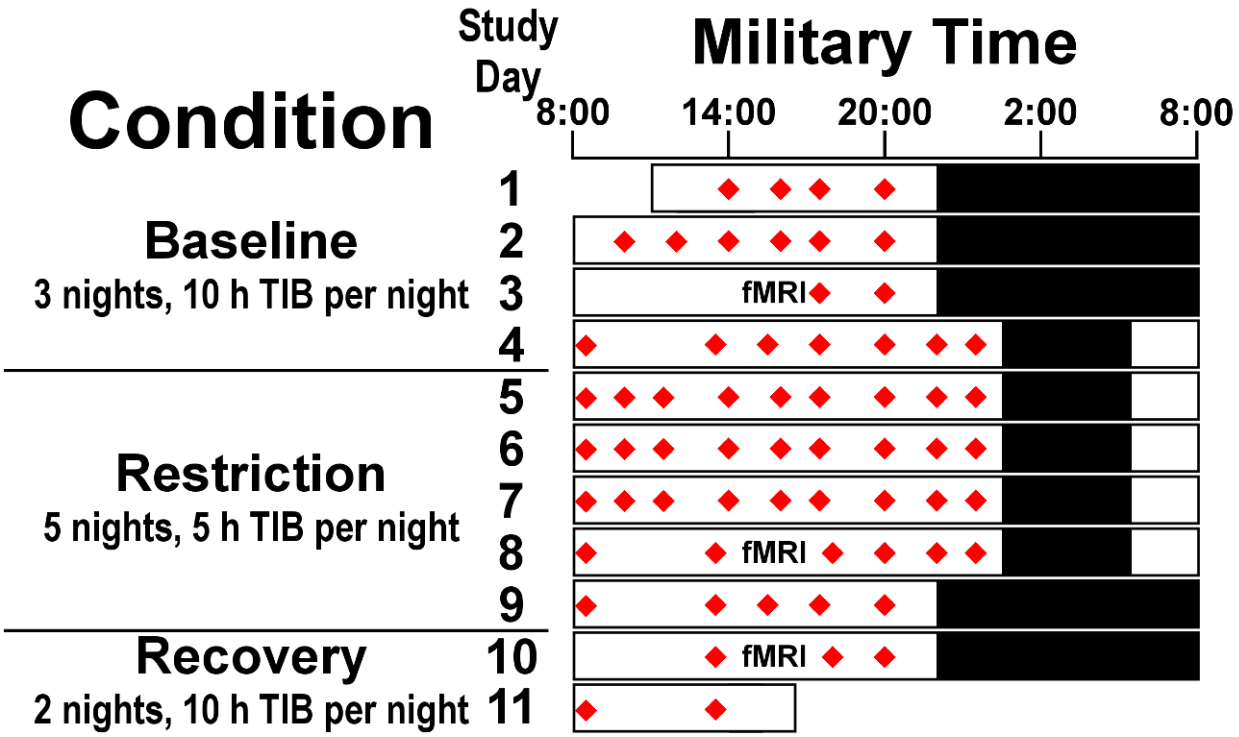


*Figure 1.* Study protocol. Each bar represents one day of an inpatient stay. White sections represent scheduled wake periods, and black sections represent scheduled sleep periods. The diagram follows a temporal sequence from left to right and top to bottom. Scheduled fMRI scans are indicated at 14:30 on the second-to-last day of each condition. Red diamonds correspond to scheduled BART administrations. The BART was given approximately every two hours during wake periods, except when collaborators had scheduled procedures for other aspects of the larger study.

## Functional Magnetic Resonance Imaging

### Equipment

Images were obtained using a Siemens 3T Magnetom Prisma Fit whole body magnetic resonance imaging (MRI) scanner with a 20-channel head coil. Visual stimuli were shown to participants in the scanner through a rearview relay mirror placed over participants' heads. The relay mirror reflected the contents shown on a projector screen behind the scanner. For the food desirability task and social threat discrimination task, participants were equipped with two-button response grips (ResponseGrip; NordicNeuroLab, Bergen, Norway) in each hand. Each response grip featured a trigger-finger button inside the curve of the grip and a thumb button on top of the grip. Participants were instructed to hold these response grips comfortably in their laps. For the incentive-modulated antisaccade task, participants' eye movements were tracked using long-range optics provided by Applied Science Laboratories (ASL). The ASL eye-tracking equipment was positioned behind the scanner and, using a camera with specialized software, monitored eye movements through the relay mirror inside the scanner. The eye-tracker was recalibrated separately for each participant and before each run of the incentive-modulated antisaccade task. Breathing rates were monitored by a pressure sensor wrapped around participants' abdomens during the food desirability task and social threat discrimination task, and a pulse oximeter was equipped during the incentive-modulated antisaccade task to measure blood oxygen saturation.

**Image Acquisition**

Participants underwent three separate scan sessions. These sessions were all scheduled to take place at 14:30 during each experimental condition, occurring after the second night of the in-lab baseline condition, after the fourth night of the sleep restriction condition, and after the first night of the sleep recovery condition (Figure 1). During each scan session, participants completed the food desirability task, social threat discrimination task, and incentive-modulated antisaccade task, in that order.

At the start of the first scan session, a structural image of the participant's brain was obtained using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) with a 2.3 sec repetition time (TR), 2.32 ms echo time (TE), 240 mm field of view (FOV), an 8° flip angle, and 0.9 $mm^3$ voxels. For each of the behavioral tasks administered during the scan session, images were acquired using an echo planar imaging (EPI) sequence with a 1.5 sec TR, 25 ms TE, 200 mm FOV, a 70° flip angle, 25 slices per TR, and 3.1x3.1x4.0 mm voxels. Each scan session also included field mapping to correct for local field inhomogeneities in subsequent analysis.

**Image Processing**

Image preprocessing and statistical analyses were done using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). Images were first corrected for slice timing differences within each volume such that each slice was aligned to the beginning of the TR. TRs were automatically removed if the Euclidean norm of the TR's motion parameters exceeded 0.5 mm of motion or if 10% of the voxels were statistical outliers as defined by a standard AFNI equation, which is based on the median absolute deviation of the time series within each voxel. Next, images from the

anatomical dataset were aligned to those from the EPI dataset. Once aligned with the functional data, the anatomical images were then normalized to Talairach standard space. Then, for any given procedure, all brain image volumes were aligned to the third volume from the first run of that procedure. Once all alignments were completed, images were also given a 4.0 mm full-width at half-maximum Gaussian blur. Finally, masks were applied to the images such that only voxels containing brain tissue were used in subsequent analyses. The values within each voxel were also normalized such that the mean for any given run was equal to 100.

**Post Hoc Power Analyses**

Using fMRI data collected in the current study, power calculations were also conducted for statistically significant contrasts. These analyses were performed using NeuroPowerTools (http://neuropowertools.org). This method bases power calculations on the local maxima in a sample dataset and estimation of the alternative distribution (Durnez et al., 2016). Critical input parameters for these analyses included: use of t-maps, screening threshold of $p < 0.05$, one-sample test, alpha = 0.05, smoothness estimates of 8 mm for X, Y, and Z dimensions, and a 3.0 $mm^3$ voxel size.

**FMRI Data Quality**

**Missing data and data validity.** All 15 participants who completed the study also completed all three fMRI scan sessions corresponding to each of the three study conditions. However, not all of the scan sessions produced valid data for all three of the fMRI tasks. Unanticipated hardware compatibility errors caused E-Prime to crash during the incentive-modulated antisaccade task on all scans from the first two participants of the study. After fixing this problem and successfully administering the task to several

participants, hardware upgrades at the scanning facility caused new compatibility errors, resulting in the loss of all three incentive-modulated antisaccade tasks for a third participant. That same participant also had a scan session during the baseline condition that was later invalidated. This was due to the discovery that the participant had poor vision and could not clearly perceive task stimuli, which was not known to investigators until after the scan. That participant was provided with MRI-safe corrective glasses closely matching the participant's prescription for subsequent scans. Lastly, the fMRI scanner itself failed midway through a scan during a recovery sleep condition, resulting in the loss of social threat discrimination and incentive-modulated antisaccade task data for that scan. This was later determined to have been caused by campus-wide water system maintenance temporarily thwarting the scanner's cooling system. Table 2 summarizes the final sample of valid datasets by task and study condition.

**Image alignment.** Co-registration of functional and anatomical brain images was performed during subject-level analyses as described in the Methods section. As a necessary step to ensure data quality, functional image overlays were manually checked against their anatomical underlays following co-registration. 26 task datasets were visibly misaligned, and 23 of these came from scan sessions during which at least one other task dataset was also misaligned, suggesting that the problem was limited only to certain scans. In total, 12 of the 44 valid scan sessions were affected, but none of the 12 scans were completed during the baseline sleep condition. Notably, anatomical images were only collected during the baseline sleep condition. Therefore, the functional images collected during these 12 affected scan sessions may have required extra correction for head movement (relative to the anatomical images)

between study conditions that was not achieved by the default co-registration function. Because the AFNI co-registration function assumes by default that the functional and anatomical images only require minor offsetting, other optional parameters (e.g., “big_move”, “giant_move”) allowing greater offsetting were incrementally tried until alignment was achieved in the remaining misaligned datasets. If alignment was still unsuccessful, then a different cost function was tried. A cost function is what is used to measure successful alignment between two images. AFNI uses a Hellinger distance cost function by default, but a local Pearson correlation cost function is recommended in the official AFNI documentation as the best alternative if the default does not work. With the local Pearson correlation cost function, all remaining datasets were successfully aligned. The Dice coefficient measuring the overlap between fully aligned functional and anatomical datasets ranged from 0.71 to 0.92 with a median of 0.88 per task run. An examination of the task runs for which this coefficient was lowest reveals that, although functional and anatomical images appear perfectly aligned, the functional images were not perfectly centered on the participants’ brains, such that the edges of these functional images were slightly cut-off. This is a problem with scanner calibration that is usually resolved by the researcher and fMRI technologist at the beginning of each scan session and cannot be corrected *post hoc*. To help better convey the problem, a midsagittal view of the single run with the worst Dice coefficient is shown in Figure 2. This particular run was missing functional data for the pons, cerebellum, and part of the occipital lobe. Because none of the affected brain structures were ROIs, this dataset was not excluded from the final analyses.

**TR censorship.** The food desirability, social threat discrimination, and incentive-modulated antisaccade tasks had 282 TRs, 316 TRs, and 380 TRs respectively (i.e., time points within a single task's fMRI data) that were collected during each scan session. As explained in Methods, no participants or scan sessions were excluded due to motion, but instead, individual TRs were censored from the final analyses if they exceeded 0.5 mm of motion or if 10% of the voxels were statistical outliers as defined by a standard equation. The percentage of TRs censored per run ranged from 0% to 44% with a median of 0.7%. Among those runs with the greatest censorship, most TRs were censored due to head motion. Overall, the median number of TRs censored for motion was 1.5, and the median number of TRs censored for exceeding the outlier limit was 2.

**Table 2. Valid fMRI Scan Sessions**

| | Baseline | Restriction | Recovery |
|---|---|---|---|
| Food Desirability Task | **14** | **15** | **15** |
| Social Threat Discrimination Task | **14** | **15** | **14** |
| Incentive-Modulated Antisaccade Task | **12** | **12** | **11** |

*Note.* Each number corresponds to the number of sessions with valid fMRI data per task and study condition.

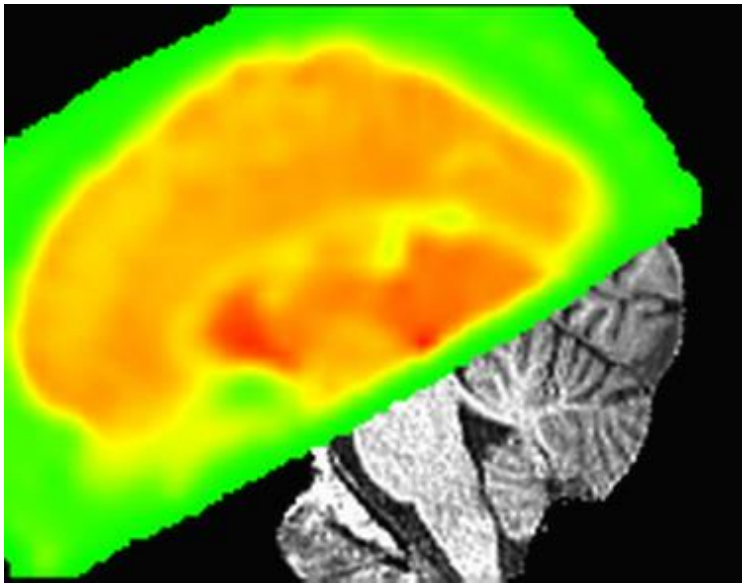

*Figure 2*. Image misalignment. Midsagittal view of the single fMRI run with the worst Dice coefficient. The functional image (green and orange) only captured part of the participant's brain. No functional data was collected for the pons, cerebellum, and most of the occipital lobe, as can be seen in the anatomical underlay (black and white). Because these missing brain regions did not contain any ROIs, this run was not excluded from final analyses.

# Chapter 3. Appetitive Desire: Methods & Results

## Food Desirability Task

### Task Description

While in the fMRI scanner, participants were shown images of various food items. First, a food item was shown by itself for 1 second on the screen. Then, over a span of 6 seconds, participants were asked to indicate the present desirability of the food item from among the following options: strongly do not want, somewhat do not want, somewhat want, and strongly want. To control for motor lateralization effects, this desirability scale and its corresponding response buttons were displayed left-to-right for half the participants and right-to-left for the other half. A fixation cross was shown for a jittered timeframe between 2.5 and 4.5 seconds (140 seconds in total across all fixation crosses in a given run) before advancing to another food item. These food items spanned several dietary categories, including sweet, salty, starchy, fruit, and dairy, which are comparable to the categorizations used in other studies on sleep and appetite (Greer et al., 2013; Spiegel et al., 2004). During each run, a total of 40 images were shown in a randomly shuffled order, with each dietary category equally represented. The precise selection of food items varied across conditions and between even- versus odd-numbered subjects in the study. The images came from a stimulus set used in previous work by Greer et al. (2013). Each day that the food desirability task was administered, participants were told in advance that a highly rated food item would be rewarded to the participant later that night.

## Behavioral Analysis

Desirability ratings from the task were scored 0-3 for each food item, spanning "strongly do not want" to "strongly want." Participants' mean desirability ratings were calculated for each food category during each of the three sleep conditions. These mean desirability ratings were separately entered into repeated measures one-way analyses of variance (ANOVAs) examining the within-subjects effects of sleep condition. This was repeated for a calorie-dense food category, a calorie-sparse food category, and the difference between them (mean calorie-dense rating minus mean calorie-sparse rating). Calorie-dense and calorie-sparse groupings were created by dichotomizing food items based on their caloric content per 100 grams, as reported by the United States Department of Agriculture's online food composition databases (https://ndb.nal.usda.gov/ndb/).

## Behavioral Results

During the rested baseline condition, participants reported somewhat or strongly wanting an average of 9.6 ± 0.8 (Mean ± SEM) calorie-dense foods and 9.6 ± 1.1 calorie-sparse foods out of the 40 foods shown in the fMRI scanner. In the subsequent sleep restriction condition, the average number of wanted calorie-dense foods was 10.2 ± 0.8, whereas the average number of wanted calorie-sparse foods was 9.9 ± 1.0. In the final sleep recovery condition, the average number of wanted calorie-dense foods returned to 9.6 ± 0.8, and the average number of wanted calorie-sparse foods was 9.4 ± 1.1. However, these changes in the reported desirability of calorie-dense foods were not statistically significant. As shown in Table 3, repeated measures ANOVAs found no effects of condition for the mean within-subject ratings of any individual food category

shown in the scanner (sweet, salty, starchy, fruit, dairy) nor for either of the caloric densities (calorie-dense, calorie-sparse) or for the difference between them (calorie-dense minus calorie-sparse).

**Table 3. Repeated measures ANOVA results for food desirability task ratings by food category**

| Food Category | Mean Baseline Rating | Mean Restriction Rating | Mean Recovery Rating | p (Effect of Condition) |
|---|---|---|---|---|
| Sweet | 1.60 | 1.79 | 1.78 | 0.313 |
| Salty | 1.45 | 1.50 | 1.27 | 0.207 |
| Starchy | 1.35 | 1.39 | 1.49 | 0.498 |
| Fruit | 1.51 | 1.53 | 1.41 | 0.472 |
| Dairy | 1.11 | 1.03 | 1.08 | 0.703 |
| Calorie Dense | 1.42 | 1.50 | 1.50 | 0.648 |
| Calorie Sparse | 1.39 | 1.40 | 1.32 | 0.598 |
| Calorie Dense > Sparse | 0.03 | 0.10 | 0.18 | 0.276 |

*Note.* Calorie-dense and calorie-sparse categories were created by dichotomizing food items based on their caloric content. n = 14.

**BOLD Signal Deconvolution**

Using AFNI's 3dDeconvolve program, trial-related activity was estimated using ordinary least squares regression. This was done separately for each participant at each scan session to produce voxel-wise statistical parametric maps. For the food desirability task, three general linear models were separately tested. The first of these included a single regressor of interest representing the onset times of food stimuli, convolved with a 7-second (stimulus duration) hemodynamic response function ("unmodulated" scheme). The second included a regressor of interest representing the onset times of food stimuli registering "somewhat want" and "strongly want" behavioral responses and another regressor for onset times of food stimuli registering "somewhat do not want" and "strongly do not want" behavioral responses. Each of these two regressors was convolved with a 7-second (stimulus duration) hemodynamic response function. Additionally, each hemodynamic response function was modulated from 1 ("somewhat want" or "somewhat do not want") to 2 ("strongly want" or "strongly do not want"), corresponding to behavioral responses for both the "wanted" regressor and the "not wanted" regressor ("1-2 modulated" scheme). This approach was contrasted with a final model, based on the analysis reported by Greer et al. (2013). The final model included a single regressor of interest representing all stimulus onsets and for which the hemodynamic response functions were modulated on a scale from 1 to 4, corresponding to the range from "strongly do not want" to "strongly want" behavioral responses ("1-4 modulated" scheme). Analyses also included regressors of no interest modeling translational and rotational motion (x, y, z, roll, pitch, yaw), motion derivatives, and baseline, linear, and non-linear trends, all estimated using AFNI's 3dvolreg.

## Hypothesis-Driven Analysis

From the resulting parametric maps, mean beta estimates were extracted for each ROI, defined as a 5 mm sphere centered at spatial coordinates identified from prior literature (Table 1). Then, the mean beta estimates within each ROI were averaged across all participants for a given sleep condition and entered into repeated measures ANOVAs examining the within-subject effect of condition for each ROI. For each of the three previously discussed modulation schemes (unmodulated, 1-2 modulation, and 1-4 modulation), five ROIs from the food desirability task were analyzed, collectively amounting to fifteen ANOVAs.

## Hypothesized ROI Results

For each of the three sleep conditions, mean activation parameters were extracted from the ROIs as defined *a priori* (Table 1). Extracted parameters are depicted in Figures 3-9. The effect of sleep condition on ROI activation was then tested in a series of repeated measures ANOVAs. However, none of the hypothesized ROIs revealed a significant effect of sleep condition. It should be noted that, contrary to hypotheses, paired t-tests revealed a significant increase ($t(14) = -2.92$, $p = 0.011$) in unmodulated activation in the right amygdala on the food desirability task from restriction to recovery (Figure 4), but the repeated measures ANOVA found no general effect of condition. Consistent with hypothesized changes, paired t-tests also revealed a marginally significant reduction in unmodulated BOLD signal between the baseline and restriction sleep conditions in the right ACC ($t(13) = 2.13$, $p = 0.053$).

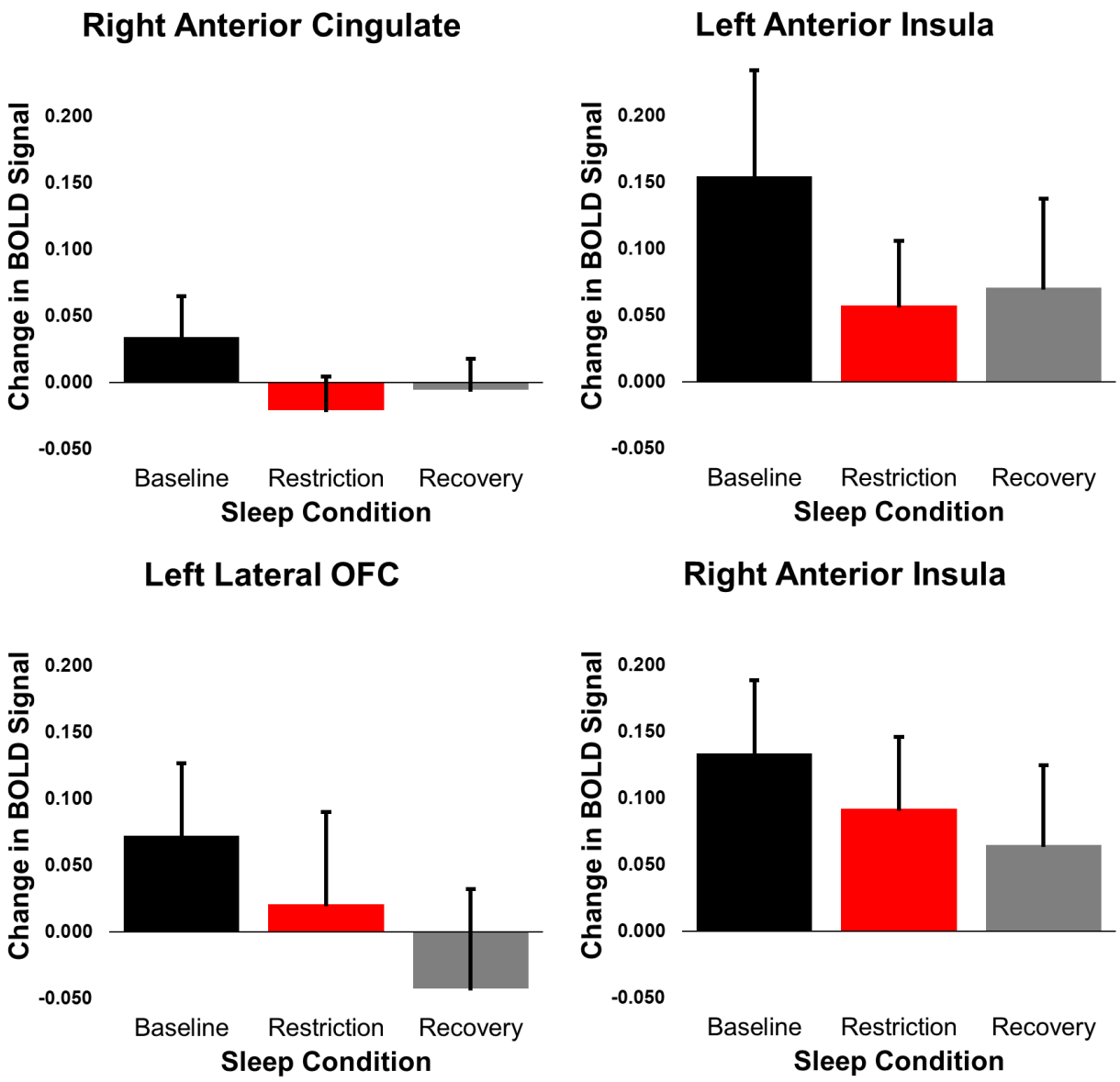


*Figure 3*. Mean (± SEM) change in unmodulated BOLD signal in cortical ROIs on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). None of the changes are significant.

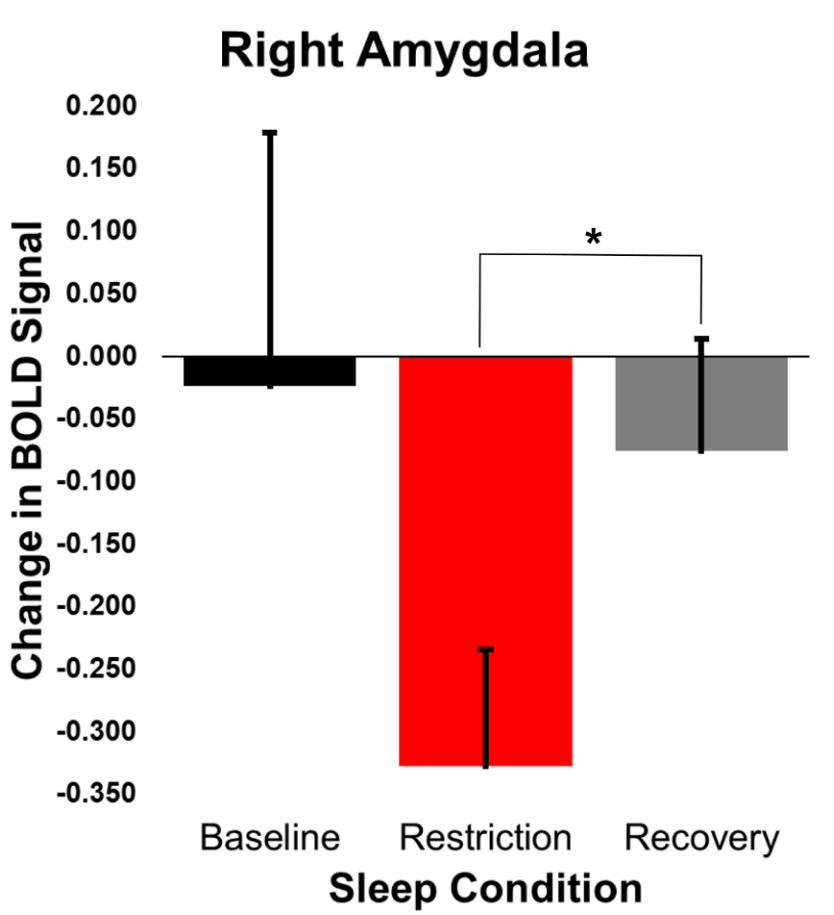


*Figure 4*. Mean (± SEM) change in BOLD signal in the right amygdala on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14).

*Note:* ***** $p < 0.05$

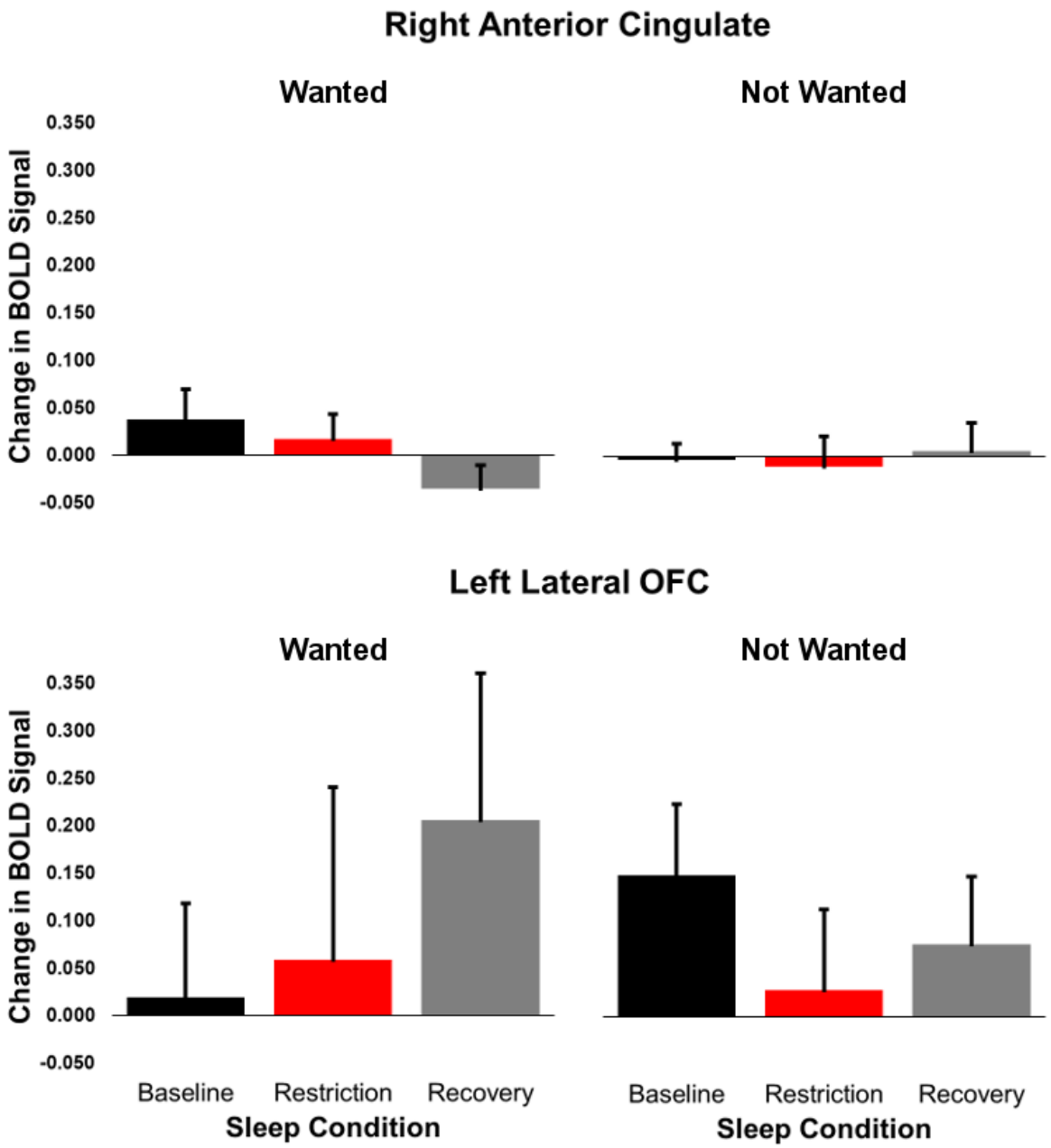


*Figure 5*. Mean (± SEM) change in 1-2 modulated BOLD signal in the right ACC and left lateral OFC on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). “Wanted” and “Not Wanted” correspond to separate regressors representing changes in BOLD signal on food stimuli that participants reported “wanting” and “not wanting,” respectively, and modulated 1-2 for “somewhat” to “strongly” reported desirability or undesirability. None of the changes are significant.

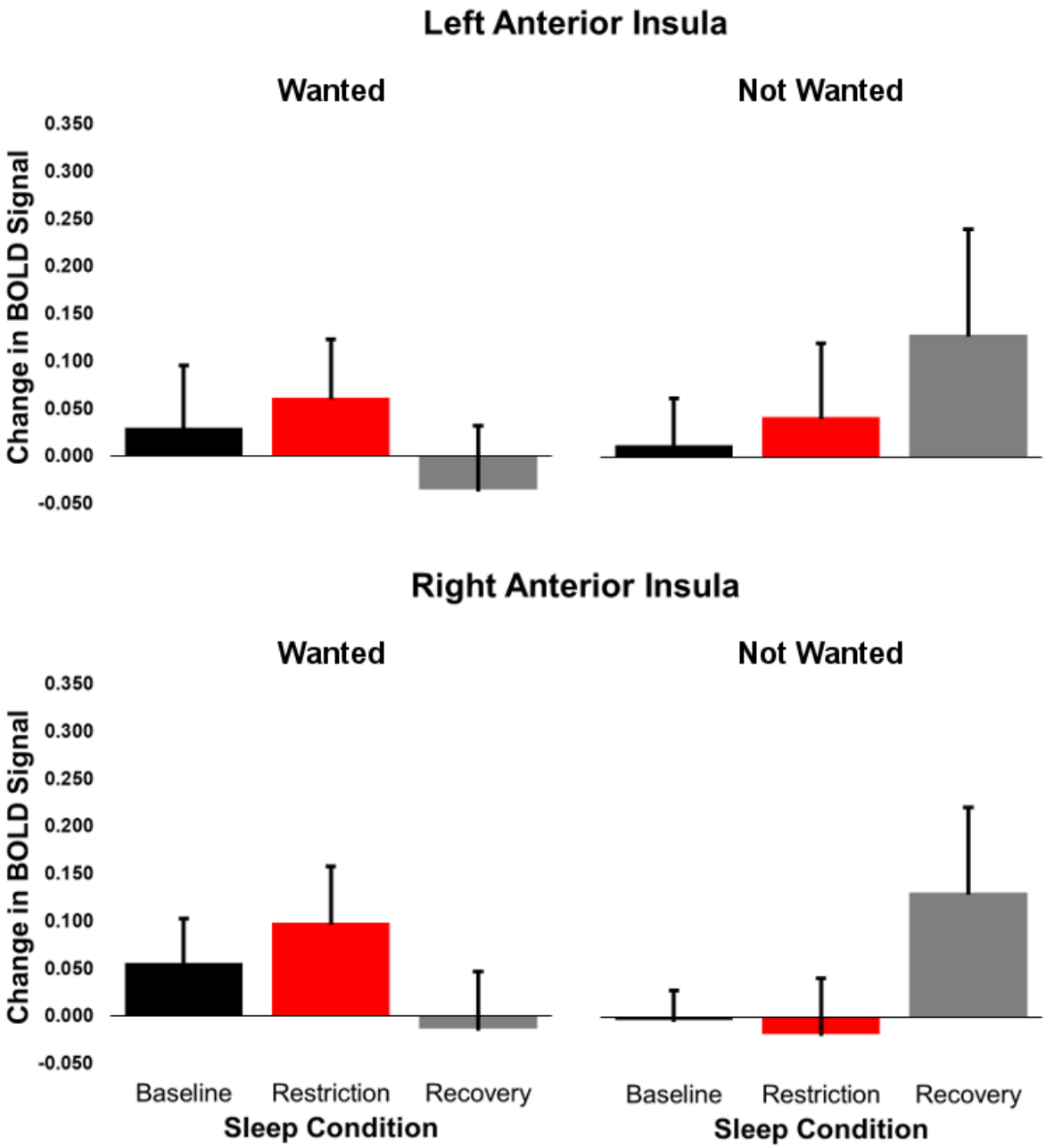


*Figure 6*. Mean (± SEM) change in 1-2 modulated BOLD signal in the left and right anterior insula on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). “Wanted” and “Not Wanted” correspond to separate regressors representing changes in BOLD signal on food stimuli that participants reported “wanting” and “not wanting,” respectively, and modulated 1-2 for “somewhat” to “strongly” reported desirability or undesirability. None of the changes are significant.

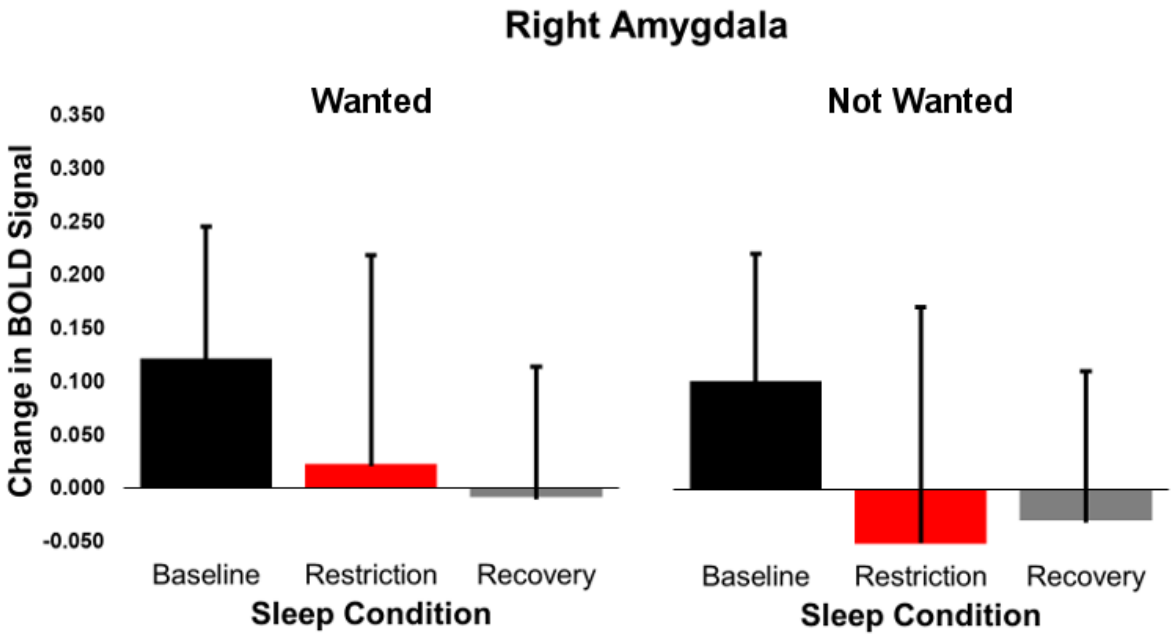


*Figure 7*. Mean (± SEM) change in 1-2 modulated BOLD signal in the right amygdala on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). “Wanted” and “Not Wanted” correspond to separate regressors representing changes in BOLD signal on food stimuli that participants reported “wanting” and “not wanting,” respectively, and modulated 1-2 for “somewhat” to “strongly” reported desirability or undesirability. None of the changes are significant.

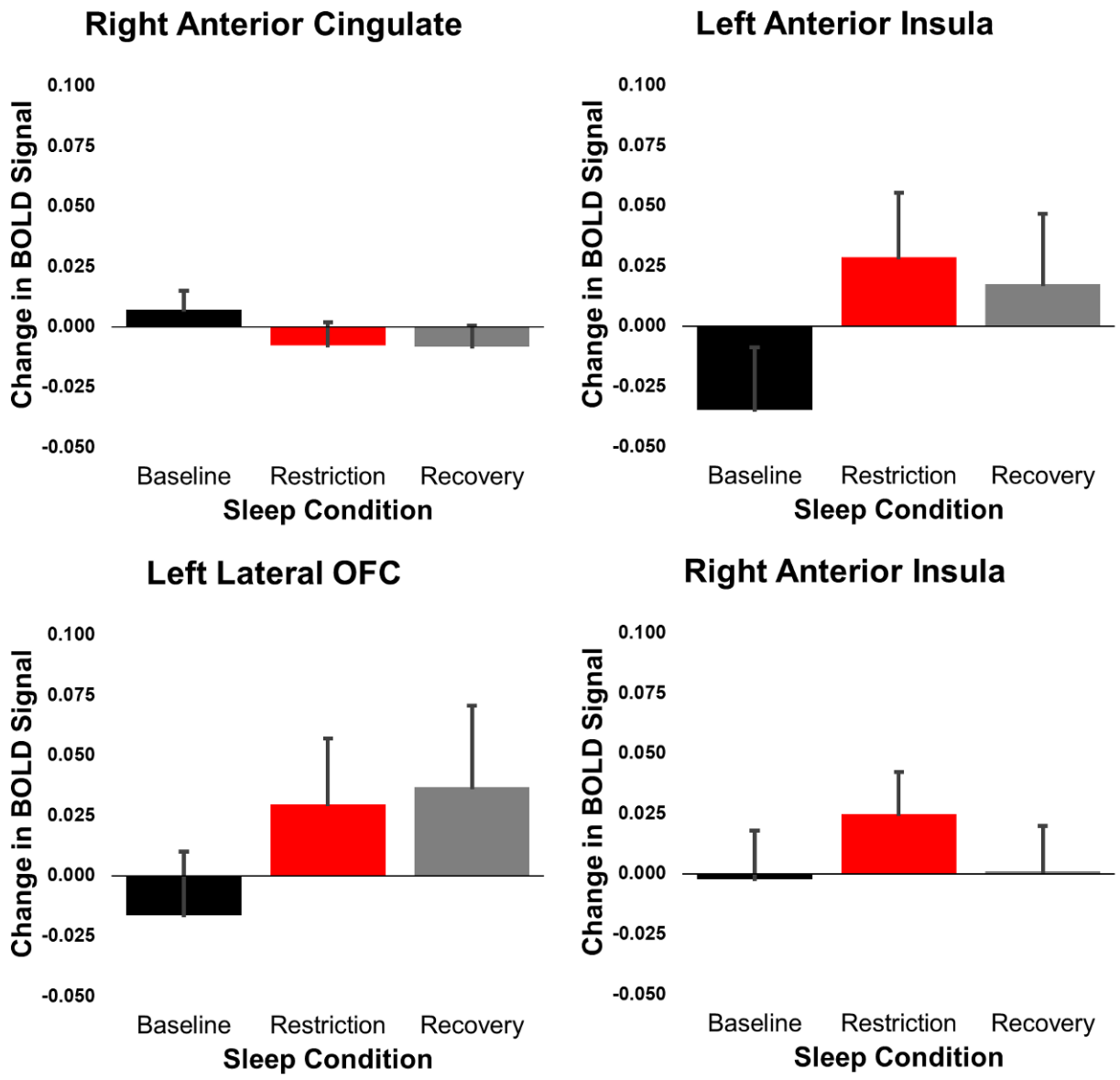


*Figure 8*. Mean (± SEM) change in 1-4 modulated BOLD signal in cortical ROIs on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). Following Greer et al. (2013), hemodynamic response functions were modulated 1-4, corresponding to participants' desirability ratings of "strongly do not want" to "strongly want." None of the changes are significant.

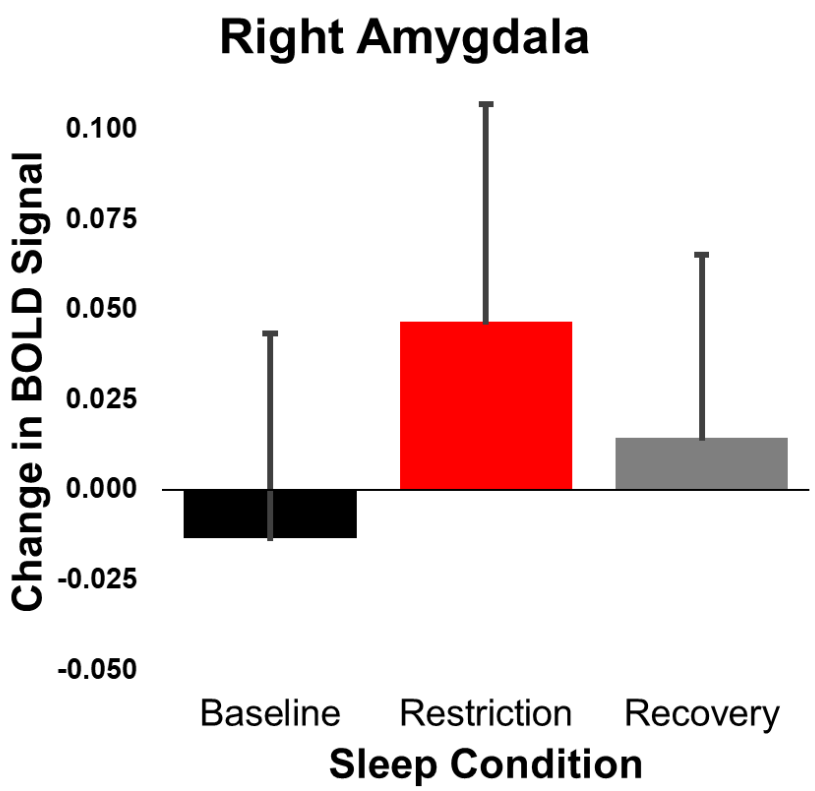


*Figure 9*. Mean (± SEM) change in 1-4 modulated BOLD signal in the right amygdala on the food desirability task during baseline, sleep restriction, and recovery fMRI scans (n = 14). Following Greer et al. (2013), hemodynamic response functions were modulated 1-4, corresponding to participants' desirability ratings of "strongly do not want" to "strongly want." None of the changes are significant.

## Exploratory Analysis

Following these hypothesis-driven analyses, group-level exploratory analyses were also conducted. Beta estimates from the initial deconvolution analyses were assessed at the group level using AFNI's 3dMVM program as part of a repeated measures ANOVA. For the food desirability task, a single factor of sleep condition (baseline, restriction, recovery) was treated as within-subject fixed effects for each of the previously discussed regressors of interest (unmodulated, 1-2 modulated "wanted", 1-2 modulated "not wanted", 1-4 modulated), with random effects of subject. Contrasts between baseline and sleep-restricted conditions in particular were examined. The number of contiguous voxels needed to correct for multiple comparisons was estimated using AFNI's recently updated spatial autocorrelation functions (in 3dFWHMx and 3dClustSim) that are now recommended (Cox et al., 2016) in order to overcome the inflated false-positive rates previously identified by Eklund, Nichols, and Knutsson (2016). Estimation parameters included the criterion that clustered voxel faces must be touching, bi-sided thresholding (i.e., testing whether voxel activation is either increased or decreased), voxel-wise $p < 0.001$, and family-wise corrected alpha = 0.05.

## Exploratory Results

None of the fMRI results from the baseline versus restriction condition contrast survived correction for multiple comparisons. However, several clusters from the baseline means map were identified, even after correcting for multiple comparisons. Activation maxima and minima were identified within each cluster. If AFNI identified more than five extrema in a given cluster, then only the five extrema with the greatest absolute magnitudes were reported (Table 4).

Three clusters were found for the unmodulated results from the food desirability task during the rested baseline condition (Table 4, Figures 10-12). Two of these clusters intersected the cerebellum. Their greatest peaks comprised an intensity of 2.537 at x = 22.5, y = -76.5, z = -15.5 in the right declive of the cerebellum and an intensity of 5.52 at x = -34.5, y = -67.5, z = -15.5 in the left declive of the cerebellum. Each of those two clusters connected the cerebellum with the occipital lobe but in the right and left hemispheres respectively. The third cluster from this task was primarily situated between the right medial and superior frontal gyri but overlapped some of the superior frontal gyrus in the left hemisphere as well. Its peak activation coordinate was in the right medial frontal gyrus with an intensity of 2.839 at x = 1.5, y = 13.5, z = 44.5. No clusters survived family-wise error (FWE) correction for either of the modulated datasets from the food desirability task.

Although none of the baseline versus restriction condition contrasts survived correction for multiple comparisons, the uncorrected results from the 1-4 modulated contrast map for the food desirability task revealed a notable point of comparison with results previously reported by Greer et al. (2013). As described in Methods, this particular group map was derived from subject-level general linear models that included a parametric regressor of participants' desirability ratings scaled 1 to 4, corresponding to "strongly do not want" to "strongly want." Crucially, this modulation scheme was consistent with the analysis reported by Greer et al. (2013). Using this alternative modulation scheme, the present analysis identified a comparable area of activation (baseline > restriction) in the ACC with voxel-wise $p < 0.05$ (Figure 13). To be clear, the precise ROI coordinates reported by Greer et al. were converted to Talairach space and

specifically tested as one of the hypothesized ROIs of the present study, but as previously explained, there was no effect of sleep restriction on this ROI in the present dataset (see Hypothesized ROI Analyses). However, the exploratory whole-brain analysis revealed an area of activation spanning part of the right ACC and right medial frontal gyrus, positioned only a few voxels posterior to the area reported by Greer et al. As expected, activation in the ACC was diminished following sleep restriction compared to baseline. However, the cluster's peak activation voxel was actually in the right medial gyrus, with an intensity of 0.215 (baseline > restriction) at x = 4.5, y = 1.5, z = 47.5, which is 12 voxels from the ROI as defined *a priori*. The *a priori* ROI is shown alongside the identified cluster in Figure 13.

**Table 4. Activation peaks in clusters surviving correction for FWE on the unmodulated food desirability task.**

| Atlas Region | Intensity | X | Y | Z |
|---|---|---|---|---|
| **Cluster 1** (479 voxels) | | | | |
| R Declive (Cerebellum) | 2.537 | 22.5 | -76.5 | -15.5 |
| R Declive (Cerebellum) | 1.754 | 7.5 | -79.5 | -12.5 |
| R Inferior Occipital Gyrus (BA 17) | 1.687 | 10.5 | -91.5 | -9.5 |
| R Lingual Gyrus (BA 18) | 1.686 | 1.5 | -94.5 | -3.5 |
| R Middle Occipital Gyrus | 1.629 | 13.5 | -94.5 | 14.5 |
| **Cluster 2** (342 voxels) | | | | |
| L Declive (Cerebellum) | 5.52 | -34.5 | -67.5 | -15.5 |
| L Cuneus (BA 17) | 3.8 | -10.5 | -97.5 | 2.5 |
| L Cuneus (BA 18) | 3.754 | -16.5 | -97.5 | -0.5 |
| L Lingual Gyrus | 3.642 | -10.5 | -85.5 | -12.5 |
| L Cuneus | 3.393 | -13.5 | -97.5 | 11.5 |
| **Cluster 3** (166 voxels) | | | | |
| R Medial Frontal Gyrus | 2.839 | 1.5 | 13.5 | 44.5 |
| R Superior Frontal Gyrus | 2.233 | 1.5 | 7.5 | 56.5 |
| R Superior Frontal Gyrus | 2.233 | 1.5 | 7.5 | 56.5 |
| R Medial Frontal Gyrus | 1.962 | 1.5 | 25.5 | 38.5 |
| L Superior Frontal Gyrus | 1.095 | -4.5 | 16.5 | 56.5 |
| L Superior Frontal Gyrus (BA 6) | 1.004 | -13.5 | 19.5 | 56.5 |

*Note.* Task activation clusters are from the baseline sleep condition (n = 14).

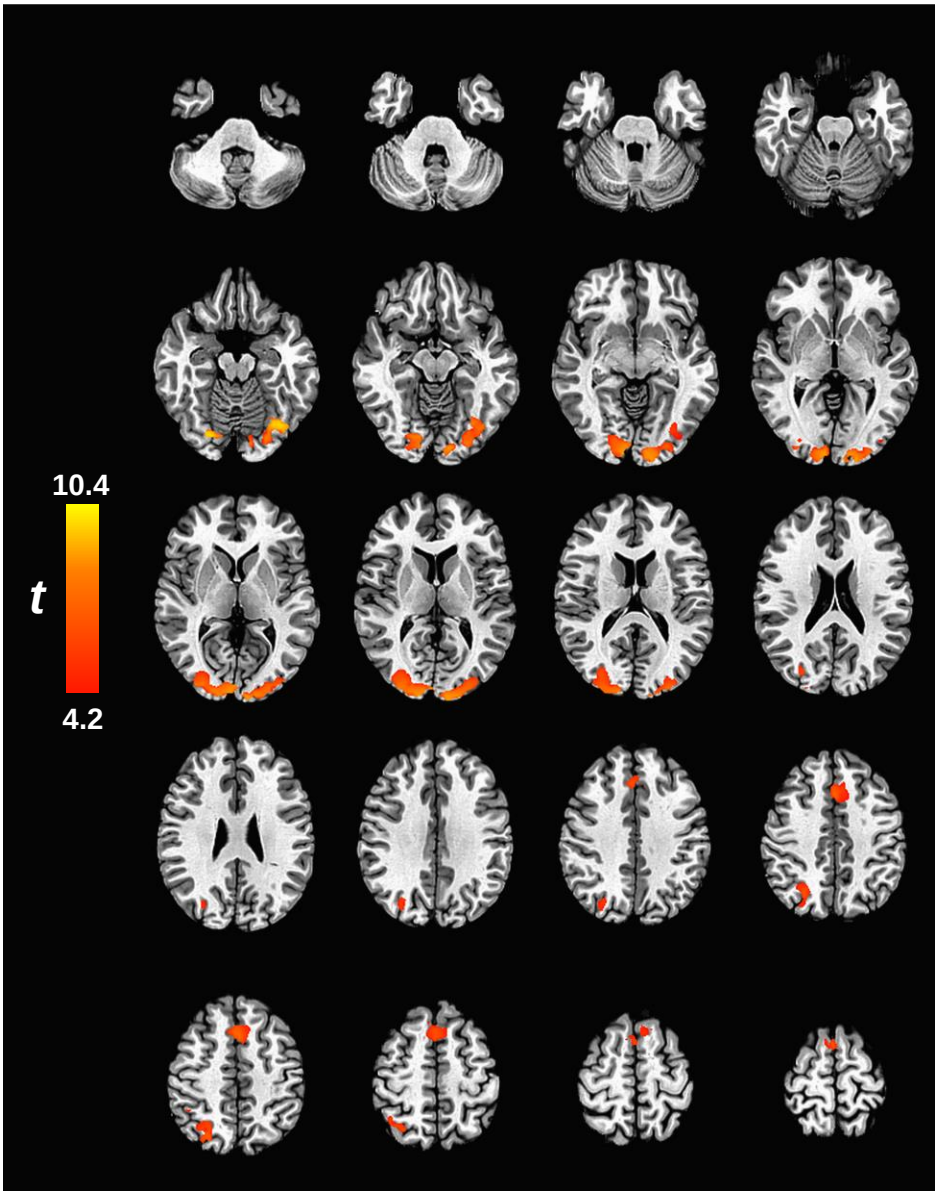


*Figure 10*. Axial view of whole-brain, unmodulated activation corrected for FWE (family-wise alpha = 0.05) on the food desirability task during the rested baseline sleep condition (n = 14). Only clusters with at least 135 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at z = 15 (ventral) and progress in increments of 5 voxels to z = 60 (dorsal) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 4.

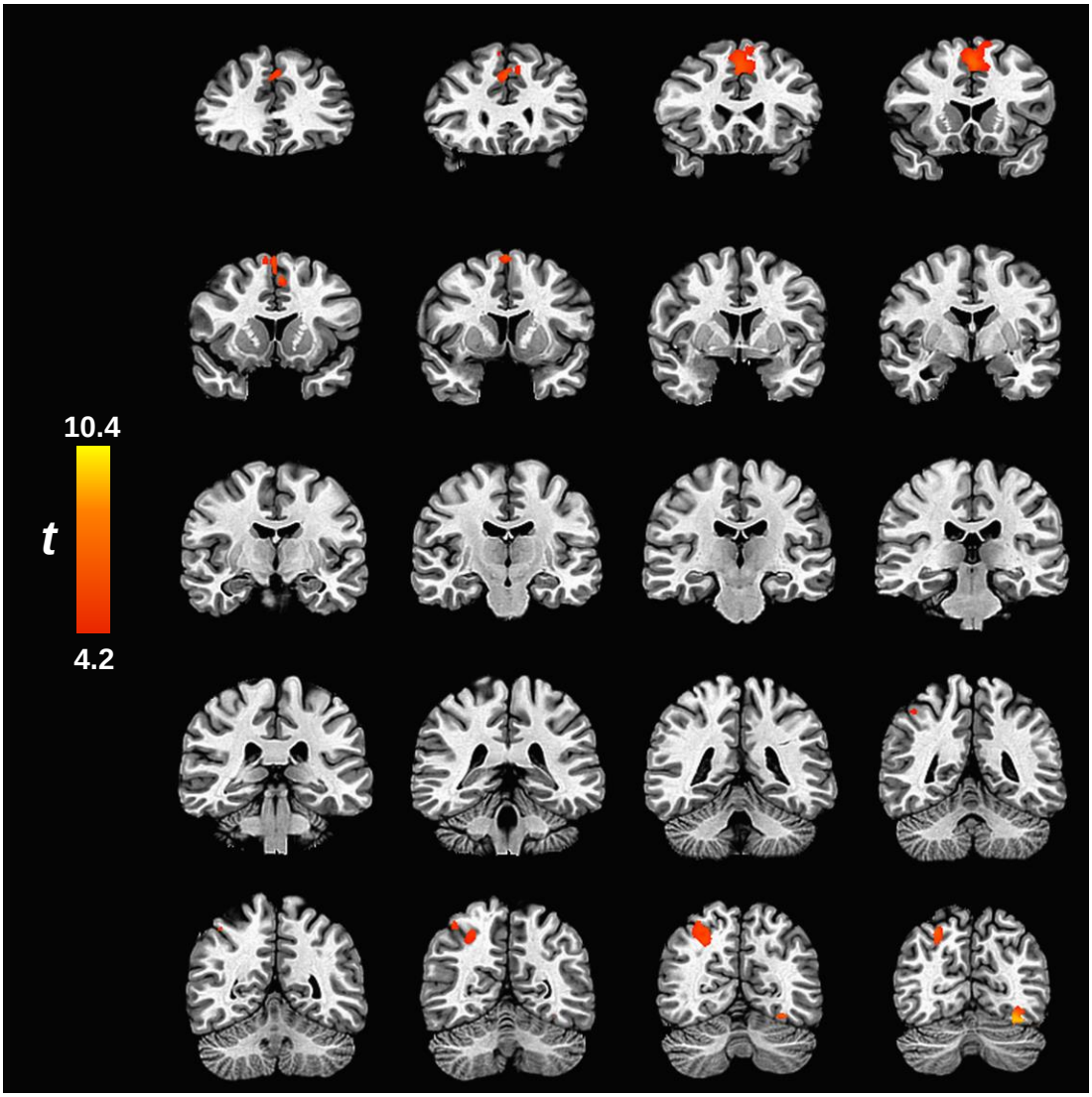


*Figure 11*. Coronal view of whole-brain, unmodulated activation corrected for FWE (family-wise alpha = 0.05) on the food desirability task during the rested baseline sleep condition (n = 14). Only clusters with at least 135 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at y = 30 (anterior) and progress in increments of 5 voxels to y = -65 (posterior) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 4.

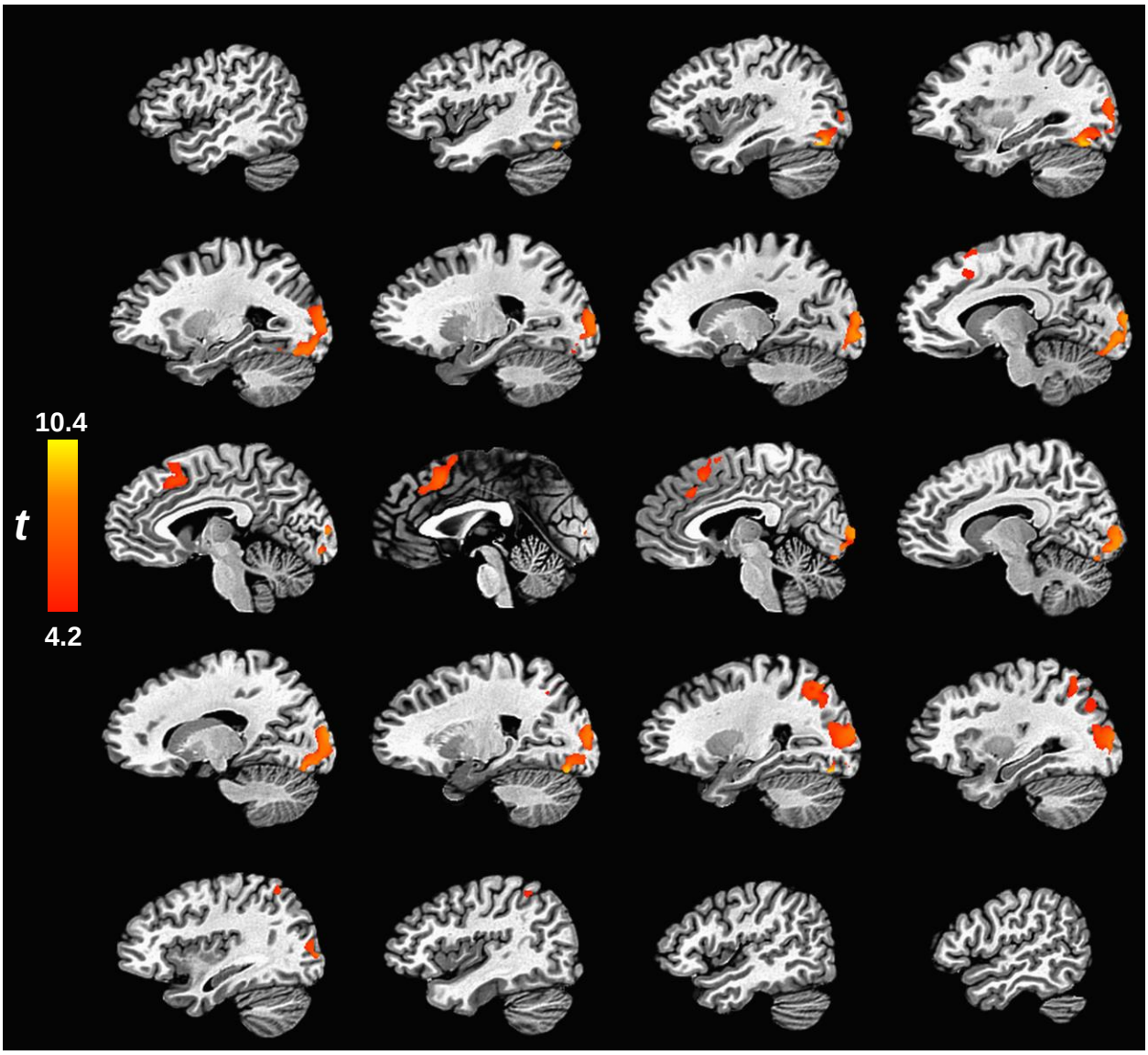


*Figure 12*. Sagittal view of whole-brain, unmodulated activation corrected for FWE (family-wise alpha = 0.05) on the food desirability task during the rested baseline sleep condition (n = 14). Only clusters with at least 135 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at x = -45 (lateral left hemisphere) and progress in increments of 5 voxels to x = 50 (lateral right hemisphere) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 4.

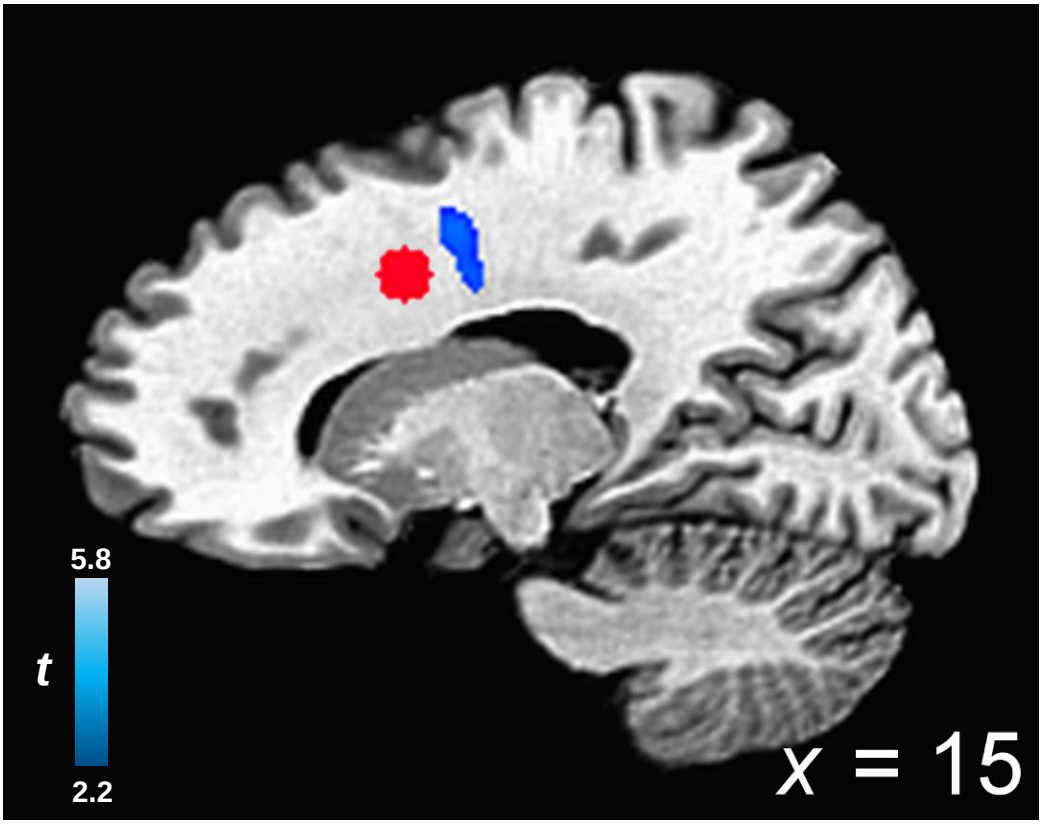


*Figure 13*. Significant 1-4 modulated BOLD signal change in the right DACC (n = 14). Sagittal view of the right DACC and right medial frontal gyrus, showing reduced activation (blue) on the food desirability task in the sleep restriction condition relative to the rested baseline condition. The DACC ROI as defined *a priori* is shown in red. Following Greer et al. (2013), hemodynamic response functions in the subject-level general linear models were modulated 1 to 4 according to the behavioral response associated with each stimulus (“strongly do not want” to “strongly want”). Voxel-wise $p < 0.05$, uncorrected for FWE.

### FMRI Power Calculation

FMRI data was used to conduct a *post hoc* power analysis, as described in Approach. This was attempted for the 1-4 modulated group map contrasting baseline > sleep restriction on the food desirability task, since this group map showed a reduction in anterior cingulate activation outside the predefined ROI at a voxel-wise $p < 0.05$. However, the power analysis never converged, indicating that the change was not large or significant enough to provide an accurate estimation. None of the other baseline versus sleep restriction contrasts yielded significant results that could be used for power analysis.

## Preprandial Appetite Questionnaires

### Questionnaire Description

Complementing behavioral data from the scanner, participants were asked to complete appetite questionnaires before and after all meals during the 11-day study. The appetite questionnaires asked participants to indicate how desirable particular categories of foods (sweet, salty, starchy, fruit, vegetables, meat, dairy) seemed at that moment. Using touchscreen mobile tablets (iPad; Apple, Cupertino, CA), responses were registered on visual-analog scales scored 0 to 100.

### Analysis

Because the appetite questionnaires inquired participants' desire for broad food categories rather than specific food items, calorie-dense and calorie-sparse food groupings were based on previous studies which have found that the calorie-dense food bias following sleep loss is most pronounced for fat- and carbohydrate-rich foods

(Benedict et al., 2012; Fang et al., 2015; Greer et al., 2013; Spiegel et al., 2004; St-Onge et al., 2014). These would roughly correspond to the sweet, salty, starchy, and dairy food categories, whereas the fruit, vegetables, and meat categories would be considered calorie-sparse. Similar to behavioral analyses on the food desirability task, preprandial appetite self-reports were averaged according to these calorie-dense (sweet, salty, starchy, dairy) and calorie-sparse (fruit, vegetables, meat) groupings, in addition to subcategory-specific responses. These averages were then analyzed in mixed effects models as a function of study condition, day into condition, and the interaction between those two, with random effects for subjects.

**Results**

In contrast with the null results from the food desirability task, behavioral data from the preprandial questionnaires revealed several significant findings. From the rested baseline condition to the sleep restriction condition, average desirability ratings decreased for each of the examined food categories (sweet, salty, starchy, fruit, vegetable, meat, dairy), regardless of caloric content. Moreover, participants on average reported greater appetite for calorie-sparse foods than for calorie-dense foods on each day of the study, regardless of sleep condition. Although responses from all days were included in this analysis, Table 5 shows only the average desirability ratings from the final days of the baseline and restriction conditions respectively, since it was hypothesized that these days would exhibit the greatest effect of sleep condition. Table 5 further summarizes the results from a linear model with fixed effects of condition, day into condition, and condition x day into condition and with random effects of subjects.

A significant effect of sleep restriction was found for the salty (Beta = -8.83, 95% CI = -17.51 to -0.16, Standard Error = 4.43, p = 0.046), fruit (Beta = -13.37, 95% CI = -22.03 to -4.71, Standard Error = 4.42, p = 0.002), vegetable (Beta = -20.69, 95% CI = -29.41 to -11.96, Standard Error = 4.45, p < 0.001), meat (Beta = -13.38, 95% CI = -21.87 to -4.88, Standard Error = 4.33, p = 0.002), and dairy (Beta = -23.09, 95% CI = -32.75 to -13.44, Standard Error = 4.93, p < 0.001) food categories, all of which elicited diminished appetite during sleep restriction. Of these five categories, there was a significant interaction of condition by day into condition for the fruit (Beta = 3.53, 95% CI = 0.48-6.58, Standard Error = 1.56, p = 0.023), vegetable (Beta = 4.59, 95% CI = 1.52-7.66, Standard Error = 1.57, p = 0.003), and dairy (Beta = 4.16, 95% CI = 0.76-7.56, Standard Error = 1.74, p = 0.017) food categories. Although there was a significant effect of sleep restriction for the aggregate calorie-dense food category (Beta = -8.65, 95% CI = -14.41 to -2.89, Standard Error = 2.94, p = 0.003), there was also a significant effect of sleep restriction (Beta = -15.81, 95% CI = -22.17 to -9.45, Standard Error = 3.25, p < 0.001) and an interaction of sleep restriction by day into condition (Beta = 3.67, 95% CI = 1.43-5.91, Standard Error = 1.14, p = 0.001) for calorie-sparse foods.

Crucially, the aggregate difference between calorie-dense food categories and calorie-sparse food categories decreased as an effect of sleep restriction (Beta = 7.16, 95% CI = 1.46-12.86, Standard Error = 2.91, p = 0.014), whereby participants' initially strong desire for calorie-sparse over calorie-dense foods grew weaker with sleep restriction. However, this effect was driven by a comparatively larger mean difference between desire for calorie-dense and calorie-sparse foods on the first day of baseline (Mean: -14.9) relative to other days of baseline after participants had habituated to the

laboratory environment and standardized meals (Range: -5.3 to -7.9). Excluding the first day of baseline from this analysis causes the effect to disappear (Beta = 1.90, 95% CI = -5.99 to 9.79, Standard Error = 4.02, p = 0.637). Figure 14 shows the day-by-day within-subject changes in calorie-dense over calorie-sparse food preference relative to the second day of baseline.

**Table 5. Mixed effects models for preprandial questionnaire ratings by food category**

| Food Category | Baseline Ratings (Day 4) | Restriction Ratings (Day 9) | p (Restriction) | p (Day into Condition) | p (Restriction * Day into Condition) |
|---|---|---|---|---|---|
| Sweet | 63.5 | 53.0 | 0.545 | **0.013** | 0.091 |
| Salty | 57.1 | 50.6 | **0.046** | 0.931 | 0.952 |
| Starchy | 56.5 | 50.5 | 0.216 | 0.903 | 0.598 |
| Fruit | 58.2 | 55.2 | **0.002** | **0.002** | **0.023** |
| Vegetable | 61.3 | 53.3 | **<0.001** | **0.011** | **0.003** |
| Meat | 70.4 | 64.4 | **0.002** | 0.319 | 0.058 |
| Dairy | 54.8 | 44.4 | **<0.001** | **0.047** | **0.017** |
| Calorie Dense | 58.0 | 49.6 | **0.003** | 0.927 | 0.588 |
| Calorie Sparse | 63.3 | 57.6 | **<0.001** | **0.003** | **0.001** |
| Calorie Dense > Sparse | -5.3 | -8.0 | **0.014** | **<0.001** | **0.002** |

*Note.* Ratings for the following categories were averaged to determine calorie-dense preference: sweet, salty, starchy, dairy. The following were averaged to determine calorie-sparse preference: fruit, vegetable, meat. The difference between the two ("Calorie Dense > Sparse") is also reported in the table. Statistically significant p values are shown in bold. n = 15.

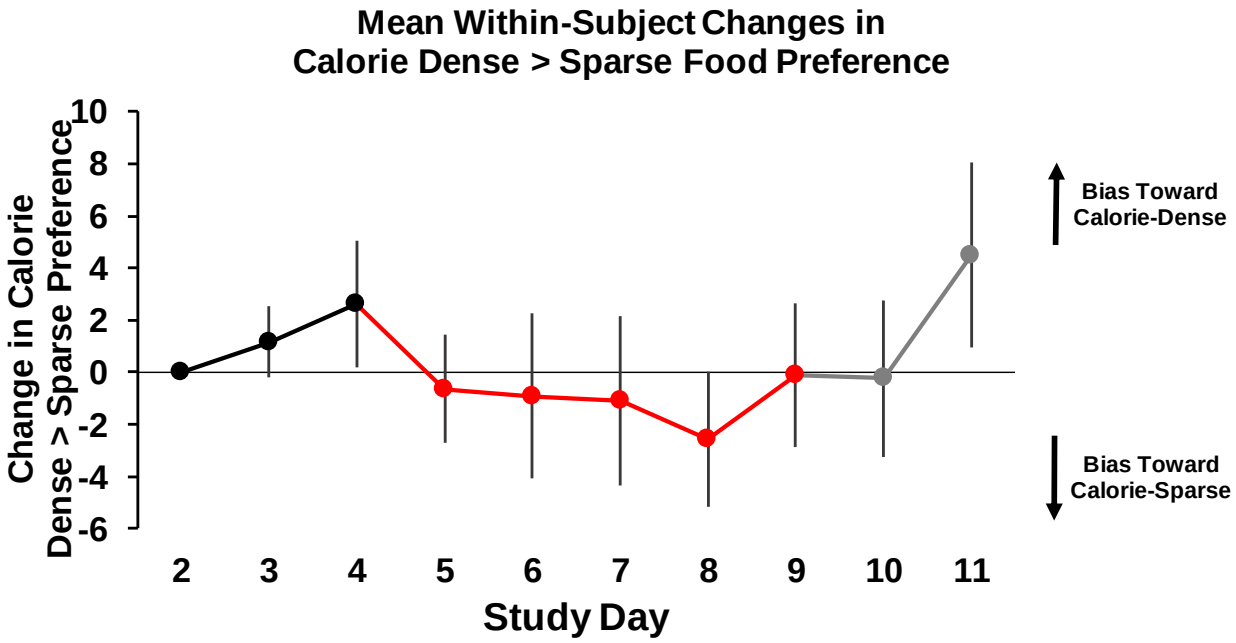


Figure 14. Mean (± SEM) within-subject changes in calorie-dense over calorie-sparse food preference, as assessed by the preprandial appetite questionnaires (n = 15). Changes during baseline (black), sleep restriction (red), and recovery (gray) are shown relative to the second day of the study. Positive changes correspond to shifts in preference toward calorie-dense foods, and negative changes correspond to shifts in preference toward calorie-sparse foods. Although not depicted, it should be noted that participants on average preferred calorie-sparse over calorie-dense foods on each day of the study.

# Chapter 4. Threat Discrimination: Methods & Results

## Social Threat Discrimination Task

### Task Description

Preceding the final night of each study condition, participants completed a social threat discrimination task (Goldstein-Piekarski et al., 2015) in the fMRI environment. In the social threat discrimination task, participants were shown a series of 3D faces displaying facial expressions that ranged from highly affiliative (i.e., non-threatening) to highly threatening. The face stimuli came from a published database of computer-generated faces that were originally produced by Oosterhof and Todorov (2008) using the FaceGen Modeler software package (http://facegen.com/) and subsequently morphed using Oosterhof and Todorov's own threat-model computer algorithms. In advance of the first scan session, participants were informed that each of these faces was procedurally morphed to create a spectrum of progressively more threatening faces. On a researcher's laptop, participants were briefly flashed a miniature spectrum of the computer-generated faces, showing "not threatening" at one end of the continuum and "threatening" at the other end of the continuum, so as to help participants understand the premise of the task. The faces were deliberately shrunk small enough and shown for only a few seconds such that participants would not have had an opportunity to study closely the details of the faces. For each run of the task, 70 face stimuli were shown in a randomized order, with 10 faces coming from each point along a 7-point spectrum of morphs. The precise selection of stimuli in each run depended on whether the current participant happened to be an even-numbered or odd-numbered

subject in the study. For each stimulus, participants were first shown a fixation cross for a jittered period of 1.3 to 2.3 seconds, with an average duration of 1.8 seconds. The equivalent of 30 null trials (a total of 201 seconds) were added to a random selection of these fixation cross periods. Next, participants were presented with a face stimulus for 1.5 seconds, after which the stimulus disappeared. Then, over the course of 2.25 seconds, participants were instructed to rate whether the face was “threatening” or “not threatening.” To control for motor lateralization effects, these two options and their corresponding response buttons were flipped left-to-right for each new participant. A blank screen followed for 0.15 seconds after each response period before advancing to the next stimulus.

**Behavioral Analysis**

The proportions of stimuli that each participant rated “threatening” were entered into repeated measures one-way ANOVAs examining the effect of sleep condition. Additionally, proportions of stimuli that each participant rated “threatening” were separately assessed for the three most threatening stimuli and the three least threatening stimuli from the 7-point stimulus morph spectrum. Repeated measures one-way ANOVAs were separately conducted for proportions of “threatening” ratings from the most threatening and least threatening ends of the stimulus morph spectrum in order to examine the effect of sleep condition.

**Behavioral Results**

Among the thirteen participants with complete data for the social threat discrimination task, a repeated measures ANOVA revealed a significant effect of condition ($F(2, 24) = 9.69$, $p < 0.001$) on the proportion of stimuli that participants rated

“threatening.” On average, participants rated “threatening” 40 ± 7% (Mean ± SD) of faces in the rested baseline condition, 33 ± 6% of faces in the sleep restriction condition, and 44 ± 9% of faces in the recovery condition (Figure 15). In paired t-tests, the sleep restriction condition was significantly different from both the rested baseline ($t(12) = 4.01$, $p = 0.002$) and recovery ($t(12) = 3.67$, $p = 0.003$) conditions, but there was no significant difference between baseline and recovery ($t(12) = 1.31$, $p = 0.214$).

Separately, repeated measured ANOVAs revealed that the effect of sleep restriction on “threatening” ratings was driven by a decreased sensitivity to stimulus morphs from the most threatening end of the stimulus morph spectrum. Specifically, there was a significant effect of sleep condition on the percent of “threatening” ratings for the most threatening stimulus morphs ($F(2, 24) = 5.57$, $p = 0.010$) but not for the least threatening stimulus morphs ($F(2, 24) = 2.00$, $p = 0.157$). In paired t-tests, the percent of “threatening” ratings for the most threatening stimulus morphs during the sleep restriction condition was significantly different from both the rested baseline ($t(12) = 2.48$, $p = 0.029$) and recovery ($t(12) = 2.79$, $p = 0.016$) conditions, but there was no significant difference between baseline and recovery ($t(12) = 0.843$, $p = 0.416$). The percent of “threatening” ratings by stimulus morph type are shown in Figure 16 for each of the three sleep conditions.

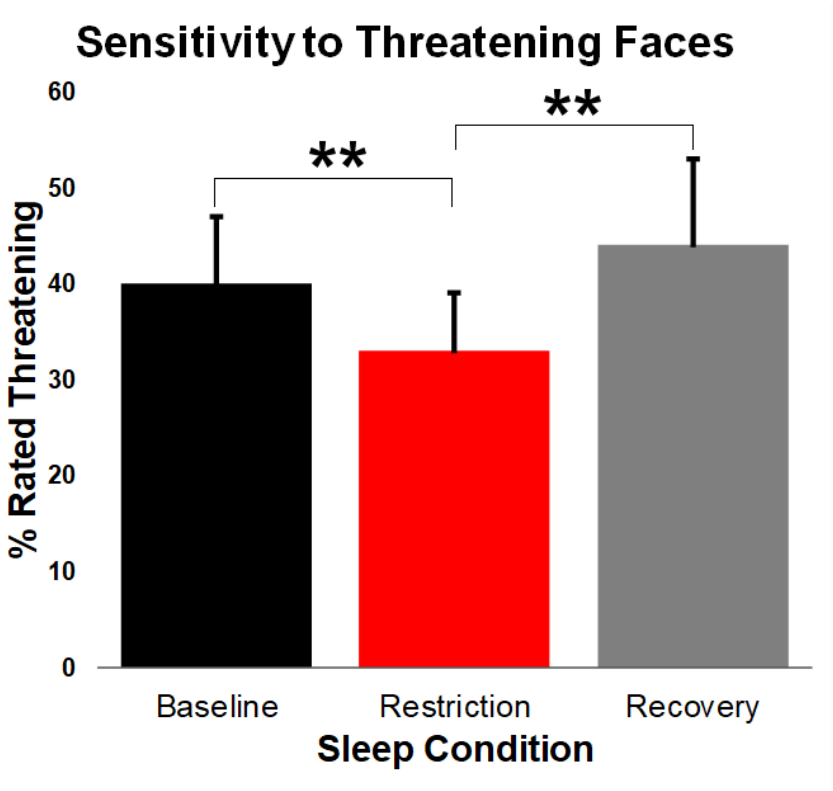


Figure 15. Sensitivity to threatening faces on the social threat discrimination task (n = 13). Bars represent the mean (± SEM) percentage of stimuli rated “threatening” during each of the three sleep conditions.

*Note:* ** $p < 0.01$

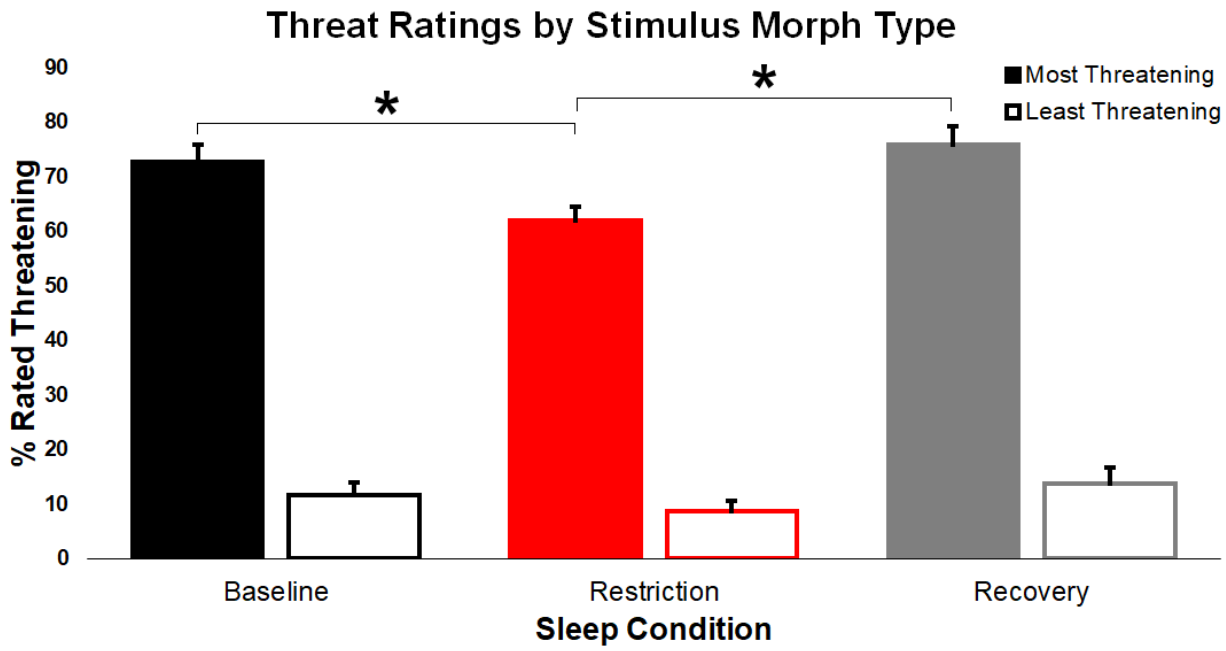


Figure 16. Threat ratings by stimulus morph type on the social threat discrimination task (n = 13). Bars represent mean (± SEM) percentage of stimuli rated "threatening" during each of the three sleep conditions. Filled and hollow bars correspond to ratings of stimulus morphs from the most and least threatening ends of the stimulus morph spectrum, respectively.

*Note:* * $p < 0.05$

**BOLD Signal Deconvolution**

Using AFNI's 3dDeconvolve program, trial-related activity was estimated using ordinary least squares regression. This was done separately for each participant at each scan session to produce voxel-wise statistical parametric maps. The general linear model included two regressors of interest representing the onset times of stimuli rated "threatening" versus "not threatening" respectively, each convolved with a 4-second (stimulus duration) hemodynamic response function. Analyses also included regressors of no interest modeling translational and rotational motion (x, y, z, roll, pitch, yaw), motion derivatives, and baseline, linear, and non-linear trends, all estimated using AFNI's 3dvolreg.

**Hypothesis-Driven Analysis**

From the resulting parametric maps, mean beta estimates were extracted for each ROI, defined as a 5 mm sphere centered at spatial coordinates identified from prior literature (Table 1). Then, the mean beta estimates within each ROI were averaged across all participants for a given sleep condition and entered into repeated measures ANOVAs examining the within-subject effect of condition for each ROI. For the social threat discrimination task, separate ANOVAs tested each of three ROI responses on stimuli rated "threatening," and separate ANOVAs tested each of three ROI responses on stimuli rated "not threatening."

**Hypothesized ROI Results**

For each of the three study conditions, mean activation parameters were extracted from the ROIs as defined *a priori* (Table 1). Extracted parameters are depicted in Figures 17-18. The effect of sleep condition on ROI activation was then

tested in a series of repeated measures ANOVAs. However, none of the hypothesized ROIs revealed a significant effect of sleep condition.

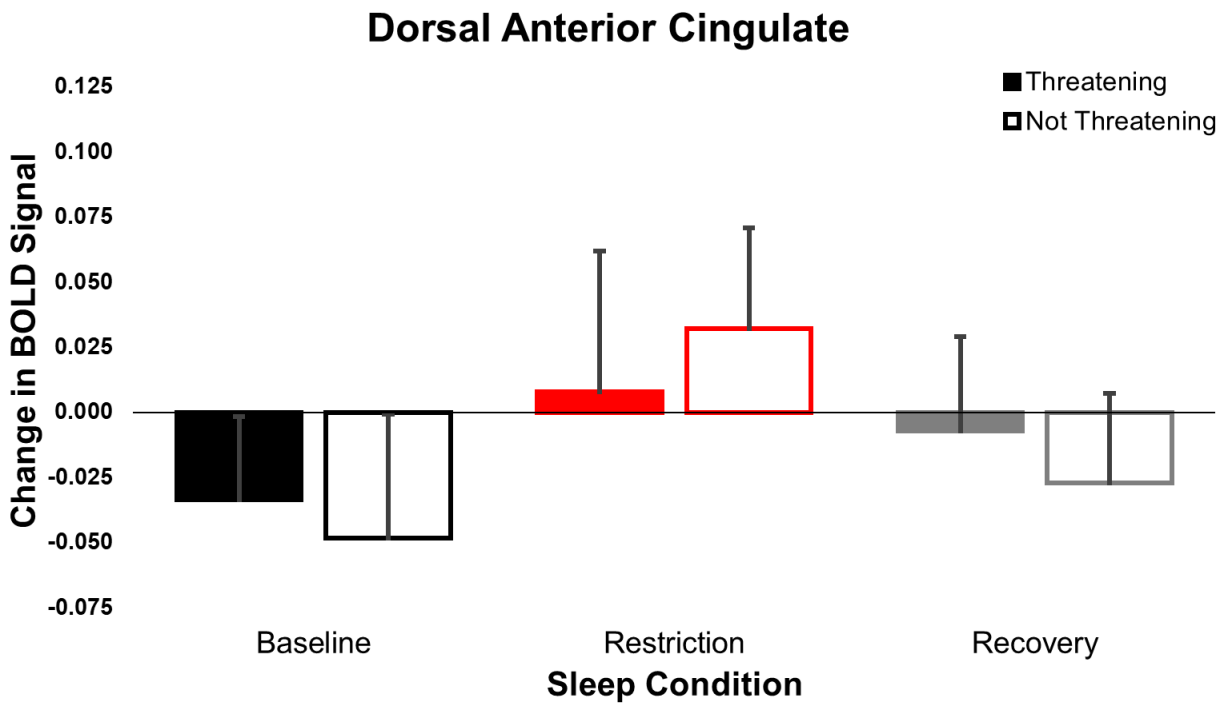


*Figure 17*. Mean (± SEM) change in BOLD signal in the DACC on the social threat discrimination task during baseline, sleep restriction, and recovery fMRI scans (n = 13). "Threatening" (filled bars) and "Not Threatening" (empty bars) correspond to separate regressors representing changes in BOLD signal on face stimuli that participants rated "threatening" and "not threatening," respectively. None of the differences between conditions or between response categories within conditions are statistically significant.

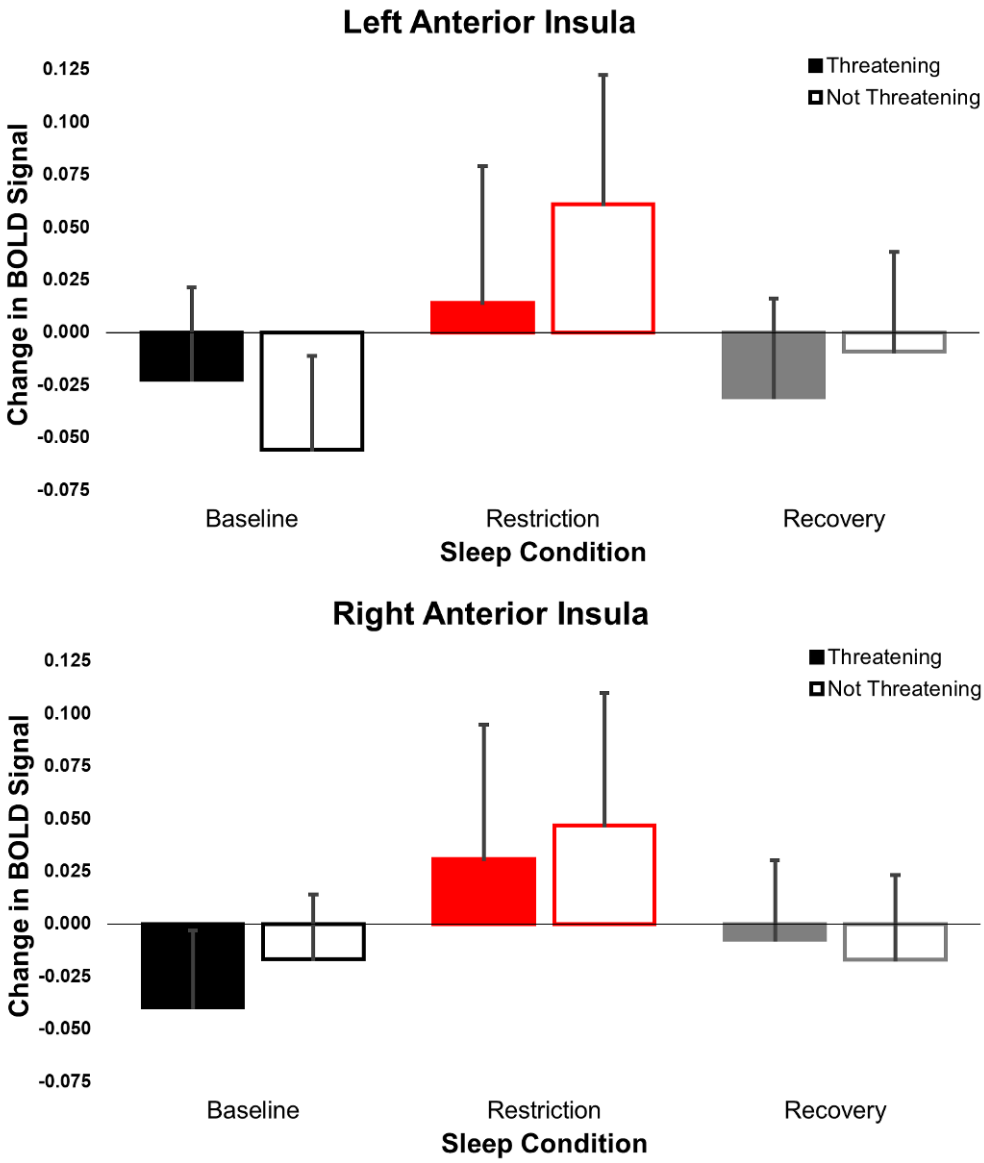


*Figure 18*. Mean (± SEM) change in BOLD signal in the left and right anterior insula on the social threat discrimination task during baseline, sleep restriction, and recovery fMRI scans (n = 13). “Threatening” (filled bars) and “Not Threatening” (empty bars) correspond to separate regressors representing changes in BOLD signal on face stimuli that participants rated “threatening” and “not threatening,” respectively. None of the differences between conditions or between response categories within conditions are statistically significant.

## Exploratory Analysis

Following these hypothesis-driven analyses, group-level exploratory analyses were also conducted. Beta estimates from the initial deconvolution analyses were assessed at the group level using AFNI's 3dMVM program as part of a repeated measures ANOVA. For the social threat discrimination task, sleep condition (baseline, restriction, recovery) and response ("threatening" versus "not threatening") were treated as within-subject fixed effects, with random effects of subject. Contrasts between baseline and sleep-restricted conditions in particular were examined. The number of contiguous voxels needed to correct for multiple comparisons was estimated using AFNI's recently updated spatial autocorrelation functions (in 3dFWHMx and 3dClustSim) that are now recommended (Cox et al., 2016) in order to overcome the inflated false-positive rates previously identified by Eklund et al. (2016). Estimation parameters included the criterion that clustered voxel faces must be touching, bi-sided thresholding (i.e., testing whether voxel activation is either increased or decreased), voxel-wise $p < 0.001$, and family-wise corrected alpha = 0.05.

## Exploratory Results

None of the fMRI results from the baseline versus restriction condition contrast survived correction for multiple comparisons. However, several clusters from the baseline means map were identified, even after correcting for multiple comparisons. Activation maxima and minima were identified within each cluster. If AFNI identified more than five extrema in a given cluster, then only the five extrema with the greatest absolute magnitudes were reported (Table 6).

An exploratory analysis was first conducted for the rested baseline group map contrasting activation during “threatening” ratings and “not threatening” ratings. No clusters from this group map survived correction for family-wise error. However, a single cluster was found in the baseline means map without contrasting response types. This cluster was situated in the right occipital lobe with a peak intensity of 0.335 at x = 7.5, y = -91.5, z = 11.5 (Table 6, Figures 19-21). Because the social threat discrimination task did not produce any statistically significant contrast maps, a *post hoc* power analysis was not pursued for this task.

**Table 6. Activation peaks in clusters surviving correction for FWE on the social threat discrimination task.**

| Atlas Region | Intensity | X | Y | Z |
|---|---|---|---|---|
| **Cluster 1** (130 voxels) | | | | |
| R Cuneus | 0.335 | 7.5 | -91.5 | 11.5 |
| R Cuneus | 0.233 | 19.5 | -88.5 | 8.5 |
| R Lingual Gyrus | 0.233 | 13.5 | -85.5 | -0.5 |
| R Lingual Gyrus (BA 18) | 0.191 | 10.5 | -76.5 | -0.5 |
| R Middle Occipital Gyrus | 0.18 | 31.5 | -88.5 | 11.5 |

*Note.* Task activation clusters are from the baseline sleep condition (n = 14).

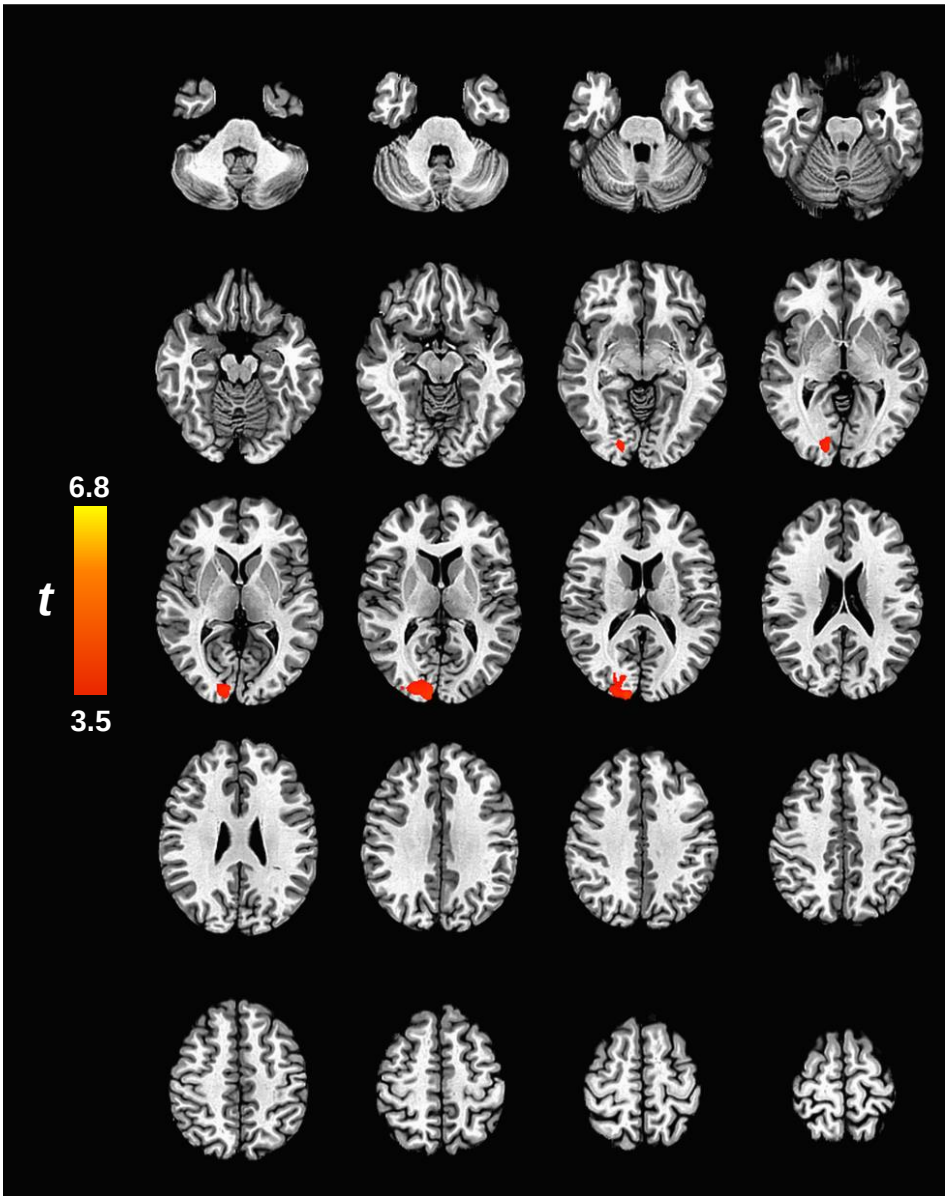


*Figure 19*. Axial view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the social threat discrimination task during the rested baseline sleep condition (n = 14). Only clusters with at least 129 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at z = -35 (ventral) and progress in increments of 5 voxels to z = 60 (dorsal) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 6.

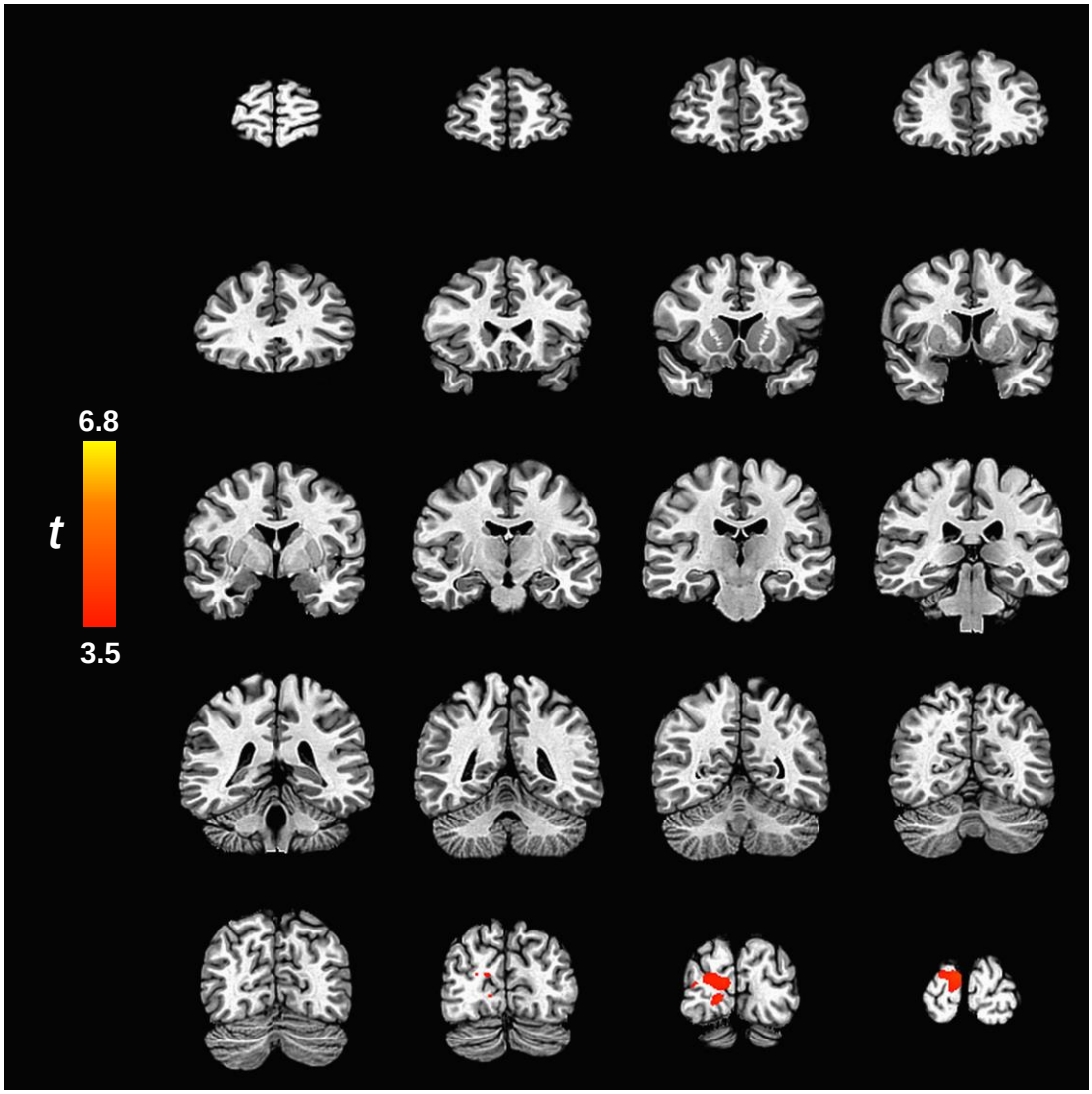


*Figure 20*. Coronal view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the social threat discrimination task during the rested baseline sleep condition (n = 14). Only clusters with at least 129 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at y = 60 (anterior) and progress in increments of 8 voxels to y = -92 (posterior) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 6.

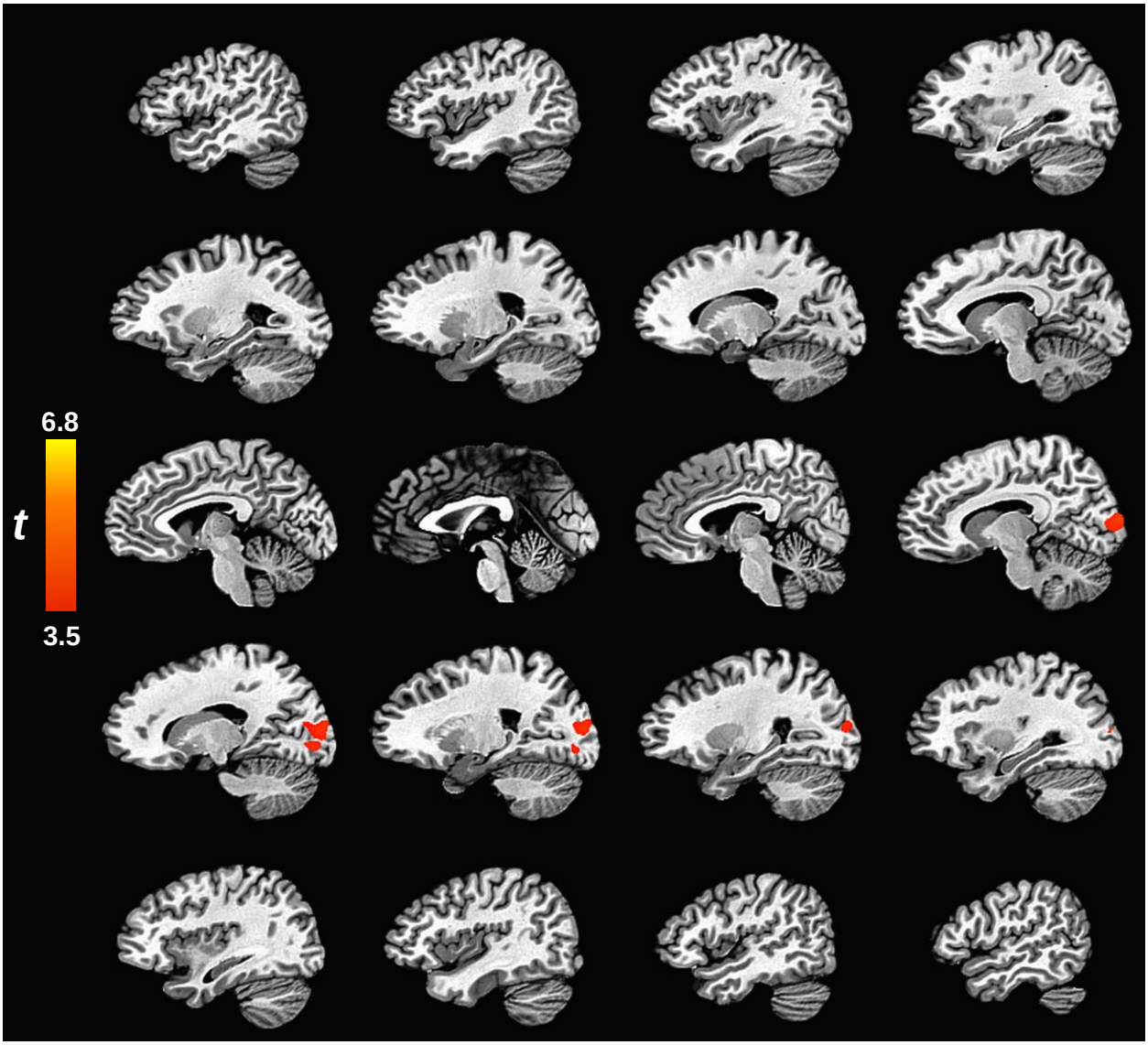


*Figure 21*. Sagittal view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the social threat discrimination task during the rested baseline sleep condition (n = 14). Only clusters with at least 129 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at x = -45 (lateral left hemisphere) and progress in increments of 5 voxels to x = 50 (lateral right hemisphere) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 6.

# Chapter 5. Incentive-Modulated Inhibitory Control: Methods & Results

## Incentive-Modulated Antisaccade Task

### Task Description

The incentive-modulated antisaccade task was divided into 6 blocks of 15 stimuli each, with different instructions preceding each block and a 30-second fixation period following each block. (Note: A block design was used to maximize the investigator's ability to localize signal change across conditions in subsequent analysis.) At first, regardless of the current block, participants were instructed to fixate on a cross in the center of a black screen. 1.925 seconds later, a bright yellow dot appeared somewhere along the horizontal axis either to the left or right of the fixation cross, and it remained on the screen for 1.5 seconds. At that point, the unique instructions of the present block came into play. Half the blocks instructed the participant to shift his or her gaze immediately to the yellow dot, and the other half instructed the participant to shift his or her gaze to the mirror opposite location of the yellow dot, relative to the fixation cross. This latter case poses a special challenge because the bright yellow dot constitutes an especially salient visual stimulus on the dark black screen. It requires self-restraint to avoid glancing at the yellow dot and instead to look deliberately in the opposite direction of the dot (Munoz & Everling, 2004). Such eye movements away from a visual stimulus are known as "antisaccades." Because antisaccades require one to suppress the urge to do otherwise, their execution reflects a psychological construct known as response inhibition, an element of inhibitory control.

This particular version of the antisaccade task was developed to assess how reward processing influences inhibitory control (Geier & Luna, 2012; Geier et al., 2010). In this version, the 6 different blocks represent all 6 combinations of one of 2 possible instruction-conditions with one of 3 possible incentive-conditions. Three of the blocks began with instructions to look away from the visual stimulus (antisaccades), and three began with instructions to look toward the visual stimulus (prosaccades). For both these instruction-conditions, three additional conditions were imposed: rewarded with points for good performance, punished with loss of points for bad performance, and neither reward nor loss. To minimize demands on working memory, crosses in the center of the screen were colored green on prosaccade blocks and red on antisaccade blocks. Additionally, the perimeter of the screen was highlighted in green on reward trials and red on loss trials.

**Behavioral Analysis**

Eye movements during the incentive-modulated antisaccade task were recorded using an Applied Science Laboratories (ASL, Bedford, MA) long-range optics eye-tracker, positioned behind the magnet. This system uses infrared light to illuminate the pupil for tracking, with a resolution of ~0.5 degrees visual angle and a sampling rate of 60Hz. A researcher simultaneously monitored the subjects' eyes via live camera feed to verify in-scanner task compliance and wakefulness. Eye-tracking data was initially scored offline using in-house scripts written in MATLAB (Natick, MA). As a backup, the E-Prime software (Psychology Software Tools, Sharpsburg, PA) in which the incentive-modulated antisaccade task was written was also used to score live performance on the task. To do this, eye-tracking coordinates were fed from the ASL eye-tracker to the E-

Prime script while the task was being completed. The E-Prime script then classified eye-tracking coordinates as belonging to either the left or right hemifield of the participant's view. Knowing the position of the on-screen target, the script then scored each trial as either correct or incorrect. Although repeated measures two-way (sleep condition and trial incentive) ANOVAs were originally planned for the eye-tracking data, that approach was hindered by a paucity of usable data. Specifically, only three participants had valid eye-tracking data for all three sleep conditions. Instead, paired t-tests were used to compare the proportions of correct responses on rewarded antisaccade trials across baseline and sleep restriction conditions. This was repeated for the proportions of correct responses on all antisaccade trials. Six participants had complete eye-tracking data for inclusion in these analyses.

**Behavioral Results**

Performance on the incentive-modulated antisaccade task was scored using the collected eye-tracking data. However, the onset and offset times of individual trials could not be parsed using the in-house MATLAB script, so the live-scored data from E-Prime were used instead (see Methods). Of the 35 scanning sessions during which valid fMRI data was collected for the antisaccade task, 18 sessions were found to have no usable eye-tracking data due to hardware and researcher error. Among the remaining 17 sessions, the number of trials with valid eye-tracking data ranged from 20 to 81 (out of 90), with a mean of 62. All invalid trials were invalidated because they failed to capture the eye trace. Of the valid trials, correct responses averaged 66 ± 4% (Mean ± SEM) on antisaccade trials and 70 ± 5% on prosaccade trials. Participants were told that correct responses on reward trials would be scored in their favor and

incorrect responses on loss trials would be scored against them. Therefore, scores were generated for each scan session by subtracting the number of incorrect responses on loss trials from the number of correct responses on reward trials. Final scores ranged from -2 to 24 with an average of 8.71 ± 1.79. Although it was expected that participants would respond differentially to rewarded antisaccade trials following sleep restriction, a paired t-test comparing baseline (Mean ± SEM: 0.67 ± 0.10) versus sleep-restricted (0.65 ± 0.09) proportions of correct responses on these trials was not statistically significant ($t(5) = 0.17$, $p = 0.874$). Disregarding incentive conditions, previous studies have reported greater error rates on the antisaccade task following sleep loss (Bocca et al., 2014; Lee et al., 2015; Meyhöfer et al., 2017). When the present comparison was expanded to include all antisaccade trials, a paired t-test still did not find any significant difference between baseline (0.67 ± 0.08) versus restriction (0.54 ± 0.04) proportions of correct responses ($t(5) = 1.18$, $p = 0.290$). Because only three participants had valid eye-tracking data for all three sleep conditions, more sophisticated analyses were not pursued. Scored eye-tracking data, including the number of valid trials per session, can be found in Table 7.

**Table 7. Eye-tracker scoring of participant performance on the incentive-modulated antisaccade task**

| Subject | Session | Valid Trials | Proportion Neutral | Proportion Reward | Proportion Loss | Proportion Prosaccades | Proportion Antisaccades | Total Proportion | Score |
|---|---|---|---|---|---|---|---|---|---|
| **1** | Baseline | 80 | 0.69 | 0.67 | 0.59 | 0.65 | 0.65 | 0.65 | 7 |
| **1** | Restriction | 81 | 0.55 | 0.64 | 0.67 | 0.56 | 0.67 | 0.62 | 7 |
| **1** | Recovery | 79 | 0.76 | 0.87 | 0.78 | 0.81 | 0.78 | 0.80 | 14 |
| **2** | Baseline | 76 | 0.79 | 0.96 | 0.96 | 0.87 | 0.95 | 0.91 | 24 |
| **2** | Recovery | 79 | 0.92 | 0.92 | 0.93 | 0.95 | 0.90 | 0.92 | 21 |
| **3** | Baseline | 20 | 0.80 | 0.71 | 1.00 | 0.63 | 1.00 | 0.85 | 5 |
| **3** | Restriction | 73 | 0.44 | 0.57 | 0.48 | 0.47 | 0.51 | 0.49 | 0 |
| **3** | Recovery | 54 | 0.69 | 0.94 | 0.86 | 0.93 | 0.74 | 0.83 | 13 |
| **4** | Baseline | 81 | 0.75 | 0.83 | 0.61 | 0.76 | 0.69 | 0.73 | 13 |
| **4** | Restriction | 31 | 0.55 | 0.73 | 0.40 | 0.81 | 0.40 | 0.61 | 8 |
| **5** | Baseline | 73 | 0.52 | 0.39 | 0.59 | 0.47 | 0.54 | 0.51 | -2 |
| **5** | Restriction | 71 | 0.77 | 0.76 | 0.67 | 0.80 | 0.67 | 0.73 | 8 |
| **5** | Recovery | 77 | 0.44 | 0.65 | 0.50 | 0.43 | 0.62 | 0.53 | 4 |
| **6** | Baseline | 69 | 0.88 | 0.83 | 0.86 | 0.93 | 0.74 | 0.86 | 16 |
| **6** | Restriction | 63 | 0.80 | 0.67 | 0.77 | 0.88 | 0.48 | 0.75 | 9 |
| **7** | Baseline | 25 | 0.33 | 0.67 | 0.50 | 0.58 | 0.38 | 0.48 | -1 |
| **7** | Restriction | 27 | 0.55 | 0.33 | 0.50 | 0.33 | 0.53 | 0.44 | 2 |
| **Mean** | | 62.29 | 0.66 | 0.71 | 0.69 | 0.70 | 0.66 | 0.69 | 8.71 |
| **SEM** | | 5.35 | 0.04 | 0.04 | 0.05 | 0.05 | 0.04 | 0.04 | 1.79 |

*Note.* All valid data are shown. Proportions refer to the proportions of correct oculomotor responses on valid trials. Proportions for neutral, reward, and loss conditions are collapsed across prosaccade and antisaccade trials. Proportions for prosaccades and antisaccades are collapsed across incentive conditions. Scores were calculated by subtracting the number of incorrect responses on loss trials from the number of correct responses on reward trials.

## BOLD Signal Deconvolution

Using AFNI's 3dDeconvolve program, trial-related activity was estimated using ordinary least squares regression. This was done separately for each participant at each scan session to produce voxel-wise statistical parametric maps. For the incentive-modulated antisaccade task, 52-second block functions were used to model responses during each of the 52-second blocks of the task. Each block (reward, loss, neutral prosaccade and antisaccade blocks) was included in the general linear model as a unique regressor. Analyses also included regressors of no interest modeling translational and rotational motion (x, y, z, roll, pitch, yaw), motion derivatives, and baseline, linear, and non-linear trends, all estimated using AFNI's 3dvolreg.

## Hypothesis-Driven Analysis

From the resulting parametric maps, mean beta estimates were extracted for each ROI, defined as a 5 mm sphere centered at spatial coordinates identified from prior literature (Table 1). Then, the mean beta estimates within each ROI were averaged across all participants for a given sleep condition and entered into repeated measures ANOVAs examining the within-subject effect of condition for each ROI. Fourteen ROIs were analyzed during antisaccade trials from the incentive-modulated antisaccade task, and the difference in ROI response between reward and neutral trials was examined for each.

## Hypothesized ROI Results

For each of the three study conditions, mean activation parameters were extracted from the ROIs as defined *a priori* (Table 1). Extracted parameters are depicted in Figures 22-25. The effect of sleep condition on ROI activation was then

tested in a series of repeated measures ANOVAs. The only significant effect of study condition on ROI activation was found in the right ventral striatum (Figure 26). Specifically, there was an effect of condition on the difference between activation during reward versus neutral antisaccade trials (reward > neutral) in the right ventral striatum ($F(2, 20) = 5.09$, $p = 0.016$). Consistent with hypotheses, this difference increased from baseline (Mean ± SEM: -0.305 ± 0.162) to restriction (0.181 ± 0.234) and decreased from restriction to recovery (-0.504 ± 0.174). Paired t-tests revealed that only the difference in activation between restriction and recovery was statistically significant ($t(10) = 2.70$, $p = 0.022$). However, the increase from baseline to restriction was marginally significant ($t(11) = -2.20$, $p = 0.050$).

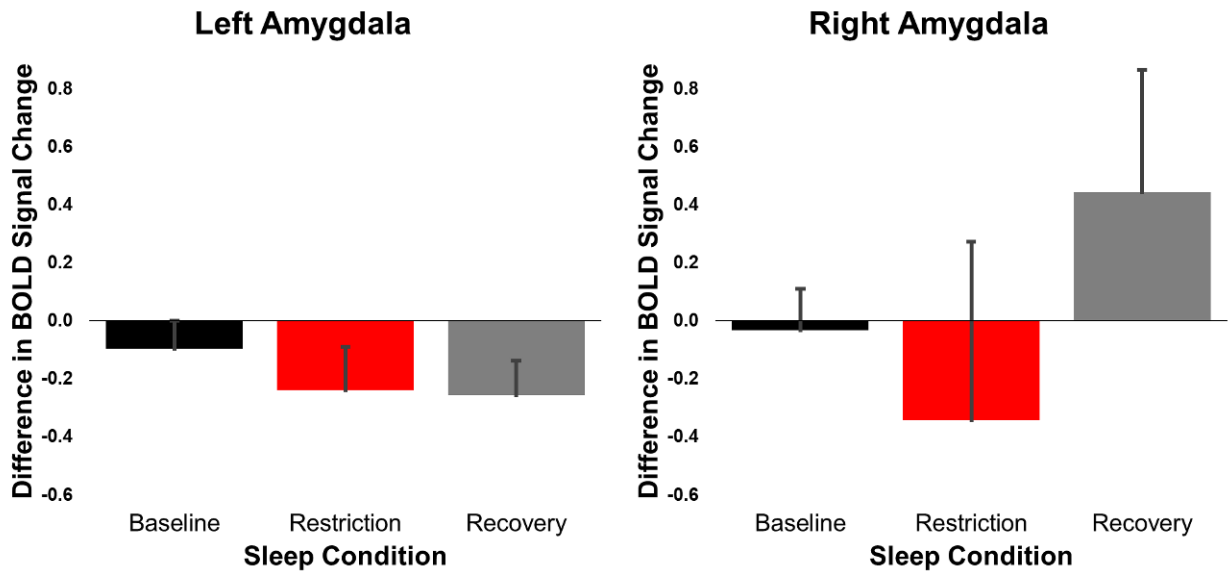


*Figure 22*. Mean (± SEM) difference in BOLD signal change on reward > neutral antisaccade trials in the left and right amygdala during baseline, sleep restriction, and recovery fMRI scans (n = 11). No significant results.

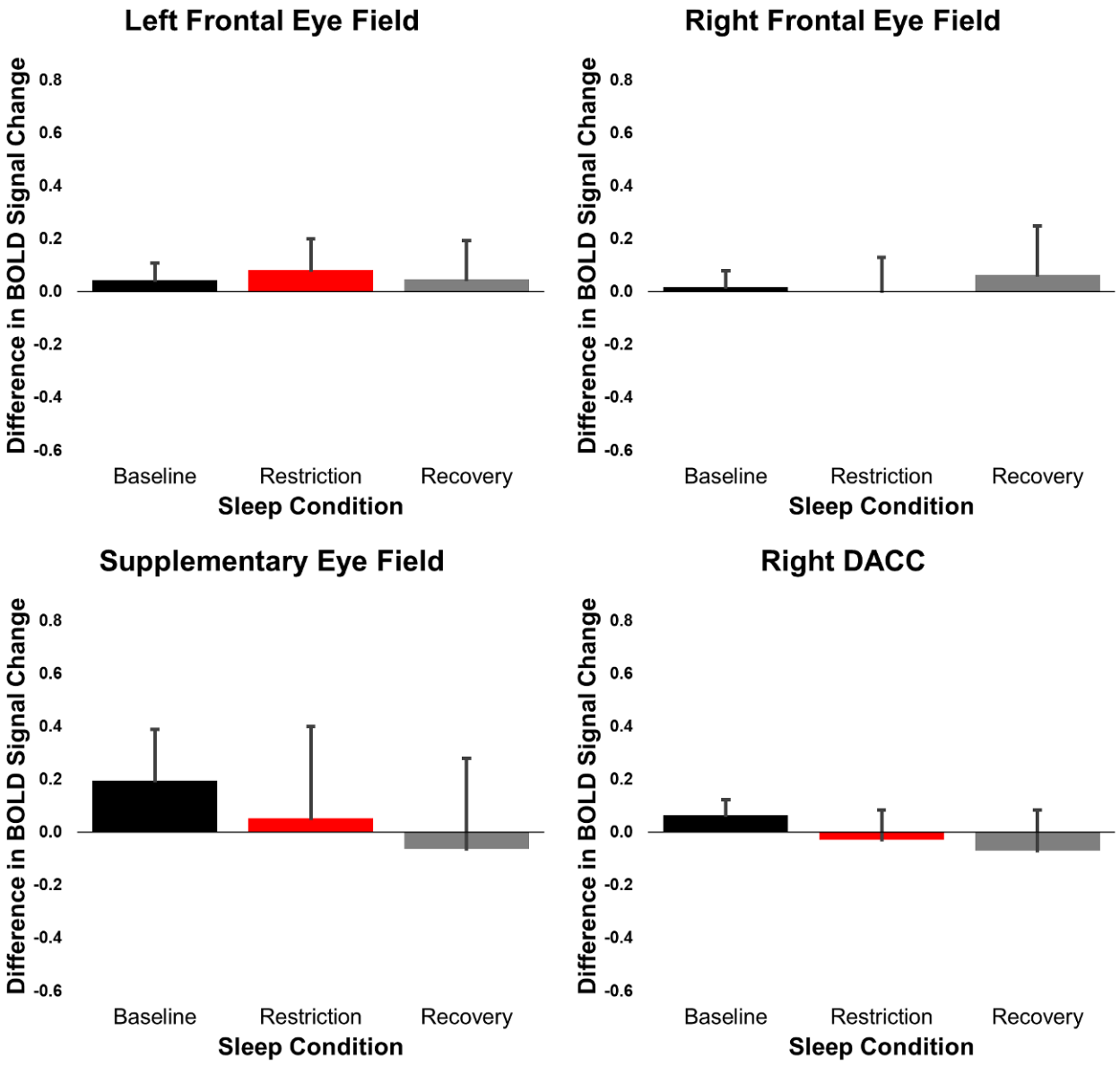


*Figure 23*. Mean (± SEM) difference in BOLD signal change on reward > neutral antisaccade trials in the FEFs, SEF, and right DACC during baseline, sleep restriction, and recovery fMRI scans (n = 11). No significant results.

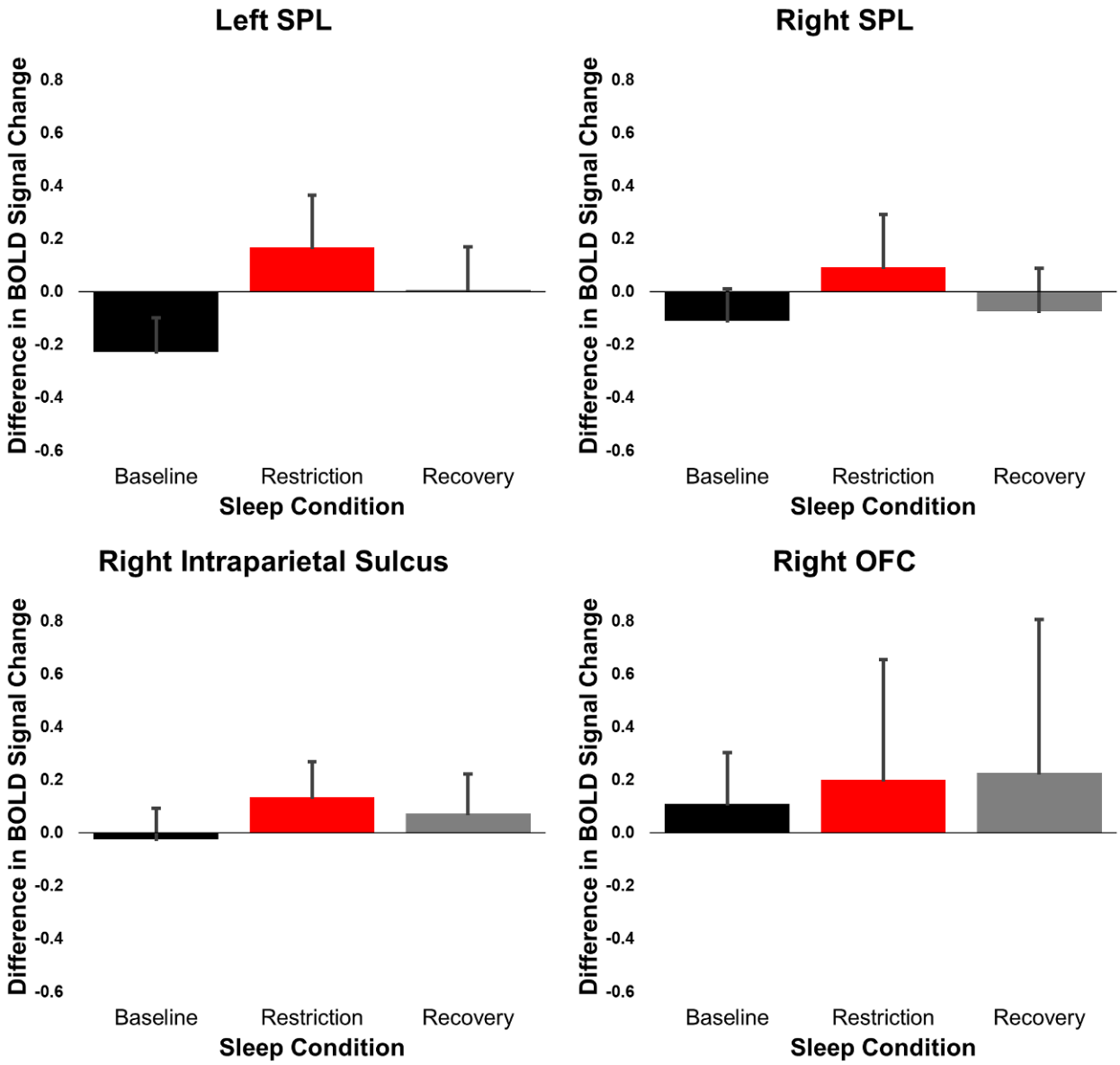


*Figure 24*. Mean (± SEM) difference in BOLD signal change on reward > neutral antisaccade trials in the SPLs, right IPS, and right OFC during baseline, sleep restriction, and recovery fMRI scans (n = 11). No significant results.

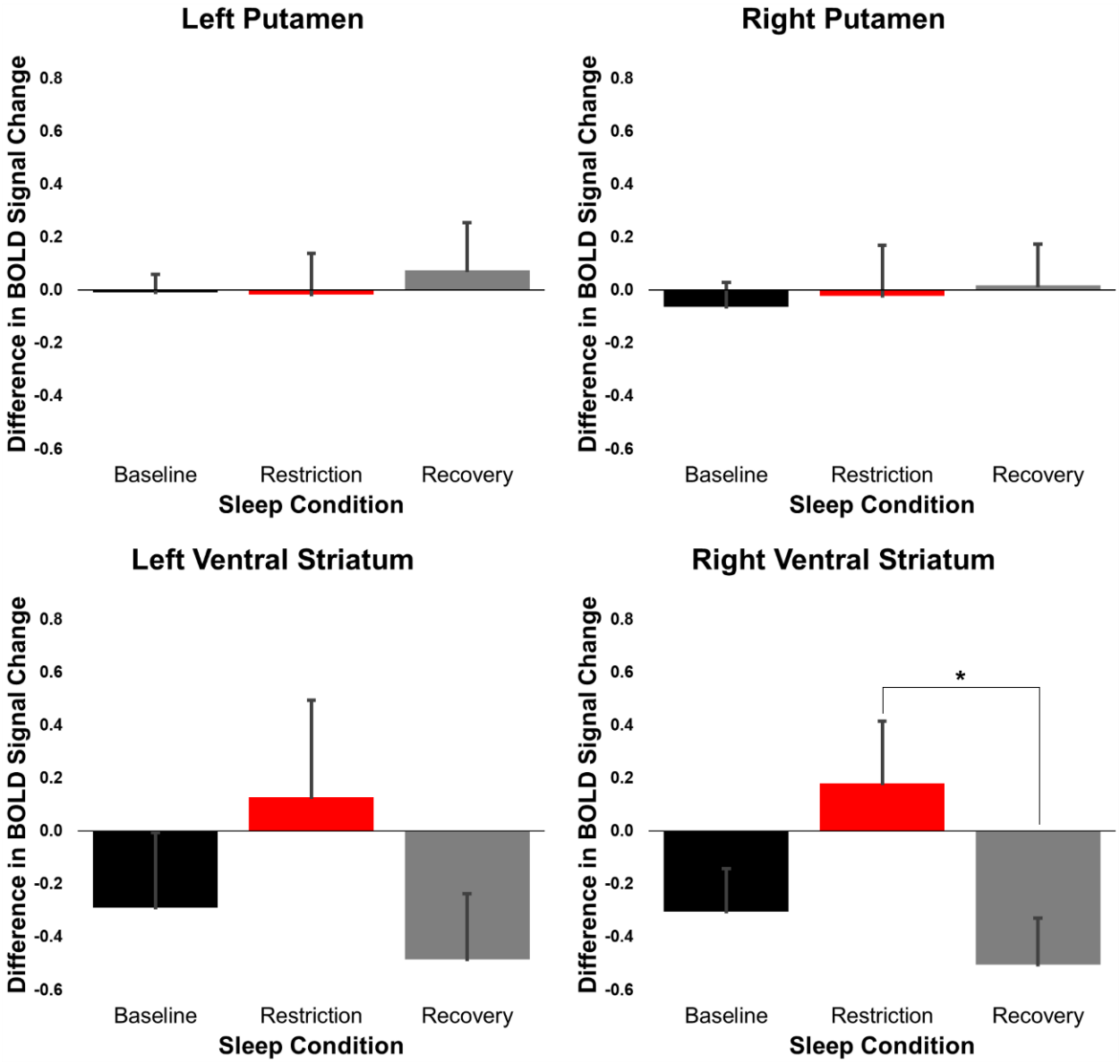


*Figure 25*. Mean (± SEM) difference in BOLD signal change on reward > neutral antisaccade trials in the putamen and ventral striatum during baseline, sleep restriction, and recovery fMRI scans (n = 11).

*Note:* ***** $p < 0.05$

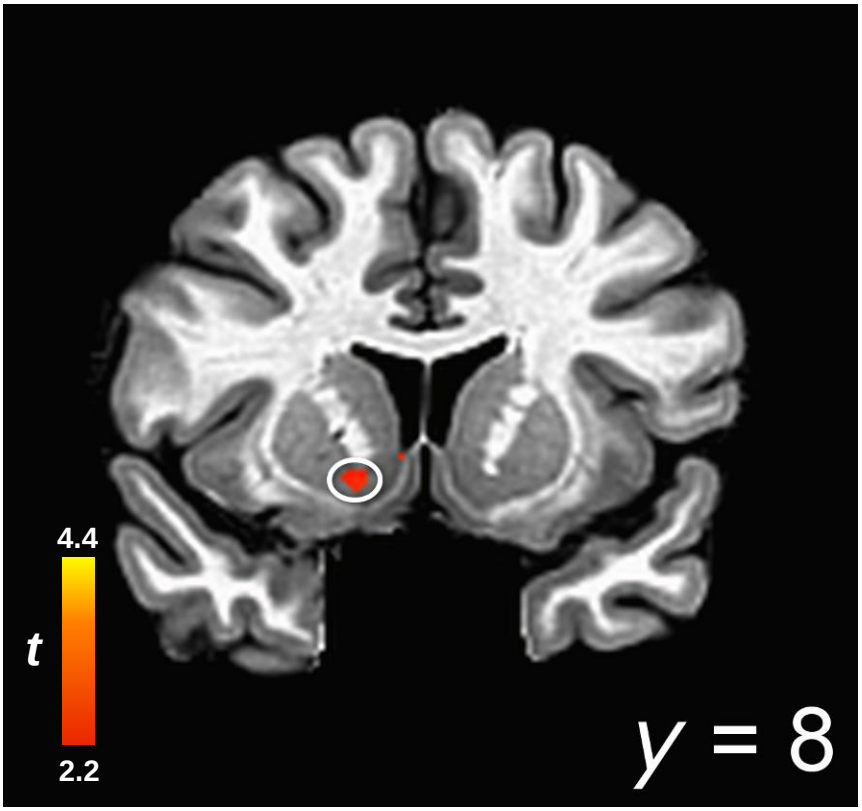


*Figure 26*. Significant BOLD signal change in the right ventral striatum (n = 11). Coronal view of the contrast in activation in the right ventral striatum ROI on reward antisaccade trials > neutral antisaccade trials during sleep restriction > rested baseline. Image taken from a whole-brain group map with voxel-wise $p < 0.05$.

## Exploratory Analysis

Following these hypothesis-driven analyses, group-level exploratory analyses were also conducted. Beta estimates from the initial deconvolution analyses were assessed at the group level using AFNI's 3dMVM program as part of a repeated measures ANOVA. For the incentive-modulated antisaccade task, the within-subject fixed effects were sleep condition (baseline, restriction, recovery), incentive (reward, loss, neutral), and instruction (antisaccade versus prosaccade), and again, the model included random effects of subject. Contrasts between baseline and sleep-restricted conditions in particular were examined. The number of contiguous voxels needed to correct for multiple comparisons was estimated using AFNI's recently updated spatial autocorrelation functions (in 3dFWHMx and 3dClustSim) that are now recommended (Cox et al., 2016) in order to overcome the inflated false-positive rates previously identified by Eklund et al. (2016). Estimation parameters included the criterion that clustered voxel faces must be touching, bi-sided thresholding (i.e., testing whether voxel activation is either increased or decreased), voxel-wise $p < 0.001$, and family-wise corrected alpha = 0.05.

## Exploratory Results

None of the fMRI results from the baseline versus restriction condition contrast survived correction for multiple comparisons. However, several clusters from the baseline means map were identified, even after correcting for multiple comparisons. Activation maxima and minima were identified within each cluster. If AFNI identified more than five extrema in a given cluster, then only the five extrema with the greatest absolute magnitudes were reported (Table 8).

Nine clusters were found for the incentive-modulated antisaccade task (Table 8, Figures 27-29). Notably, five out of the nine clusters were situated in the frontal lobe near regions well-known for their contributions to antisaccade task performance, including the FEFs, SEFs, and pre-SMA. A sixth cluster was found in the parietal lobe with a peak intensity of 7.019 at x = 1.5, y = -70.5, z = 65.5 in the right precuneus. Two more clusters were respectively situated in the left (peak intensity = 3.996, x = -46.5, y = -67.5, z = 11.5) and right (peak intensity = 2.995, x = 61.5, y = -55.5, z = 8.5) middle temporal gyri, and the final cluster spanned the right middle occipital gyrus (peak intensity = -4.856, x = 28.5, y = -94.5, z = 2.5). The largest of these nine clusters contained 6,114 voxels, connecting the dorsal frontal lobe with the basal ganglia. The two greatest activation peaks from this cluster were near the right and left FEFs, with peak intensities of 1.683 and 1.547 at x = 43.5, y = -4.5, z = 59.5 and x = -55.5, y = 13.5, z = 59.5, respectively. In contrast with the other two tasks, three of the nine clusters from the antisaccade task showed negative activation extrema (i.e., less activation during task trials than during fixation periods). In particular, two of these had activation intensities with the greatest absolute magnitudes out of any cluster and were situated in the left (intensity = -11.712, x = -28.5, y = 58.5, z = -21.5) and right (intensity = -21.475, x = 37.5, y = 55.5, z = -21.5) superior frontal gyri.

**Table 8. Activation peaks in clusters surviving correction for FWE on the incentive-modulated antisaccade task.**

| Atlas Region | Intensity | X | Y | Z |
|---|---|---|---|---|
| **Cluster 1** (6,114 voxels) | | | | |
| R Precentral Gyrus | 1.683 | 43.5 | -4.5 | 59.5 |
| L Precentral Gyrus | 1.547 | -55.5 | 13.5 | 8.5 |
| R Inferior Frontal Gyrus | 1.476 | 55.5 | 19.5 | 2.5 |
| R Lingual Gyrus | 1.441 | 4.5 | -82.5 | -9.5 |
| R Middle Frontal Gyrus | 1.436 | 55.5 | 4.5 | 41.5 |
| **Cluster 2** (2,163 voxels) | | | | |
| R Precuneus | 7.019 | 1.5 | -70.5 | 65.5 |
| L Superior Parietal Lobule | 3.783 | -7.5 | -67.5 | 59.5 |
| R Postcentral Gyrus | 3.422 | 40.5 | -46.5 | 62.5 |
| R Superior Parietal Lobule | 3.192 | 10.5 | -70.5 | 56.5 |
| L Precuneus | 3.022 | -7.5 | -61.5 | 65.5 |
| **Cluster 3** (286 voxels) | | | | |
| R Middle Frontal Gyrus | 3.249 | 34.5 | 43.5 | 38.5 |
| R Superior Frontal Gyrus | 0.954 | 19.5 | 43.5 | 41.5 |
| R Middle Frontal Gyrus (BA 8) | 0.905 | 40.5 | 25.5 | 44.5 |
| R Middle Frontal Gyrus (BA 10) | 0.855 | 37.5 | 43.5 | 23.5 |
| R Middle Frontal Gyrus | 0.702 | 40.5 | 31.5 | 26.5 |
| **Cluster 4** (257 voxels) | | | | |
| L Superior Frontal Gyrus (BA 9) | 3.561 | -28.5 | 49.5 | 35.5 |
| L Superior Frontal Gyrus | 2.754 | -37.5 | 52.5 | 32.5 |
| L Superior Frontal Gyrus (BA 10) | 2.018 | -31.5 | 55.5 | 23.5 |
| L Middle Frontal Gyrus (BA 8) | 1.695 | -40.5 | 31.5 | 41.5 |
| L Middle Frontal Gyrus | 0.888 | -28.5 | 25.5 | 32.5 |
| **Cluster 5** (209 voxels) | | | | |
| R Middle Temporal Gyrus | 2.995 | 61.5 | -55.5 | 8.5 |
| R Middle Temporal Gyrus (BA 39) | 2.849 | 55.5 | -67.5 | 11.5 |
| R Inferior Temporal Gyrus (BA 37) | 2.837 | 55.5 | -64.5 | 2.5 |
| R Middle Temporal Gyrus | 1.631 | 43.5 | -64.5 | 8.5 |
| **Cluster 6** (155 voxels) | | | | |
| L Superior Frontal Gyrus | -11.712 | -28.5 | 58.5 | -21.5 |
| **Cluster 7** (138 voxels) | | | | |
| R Superior Frontal Gyrus | -21.475 | 37.5 | 55.5 | -21.5 |
| **Cluster 8** (121 voxels) | | | | |
| R Middle Occipital Gyrus (BA 18) | -4.856 | 28.5 | -94.5 | 2.5 |
| R Middle Occipital Gyrus (BA 18) | -3.733 | 37.5 | -88.5 | 2.5 |
| R Middle Occipital Gyrus (BA 18) | -3.066 | 37.5 | -82.5 | -9.5 |
| R Middle Occipital Gyrus (BA 19) | -2.465 | 43.5 | -73.5 | -9.5 |
| **Cluster 9** (115 voxels) | | | | |
| L Middle Temporal Gyrus (BA 39) | 3.996 | -46.5 | -67.5 | 11.5 |
| L Middle Temporal Gyrus | 3.46 | -43.5 | -61.5 | 11.5 |
| L Middle Temporal Gyrus (BA 39) | 2.937 | -55.5 | -58.5 | 11.5 |

*Note.* Task activation clusters are from the baseline sleep condition (n = 12).

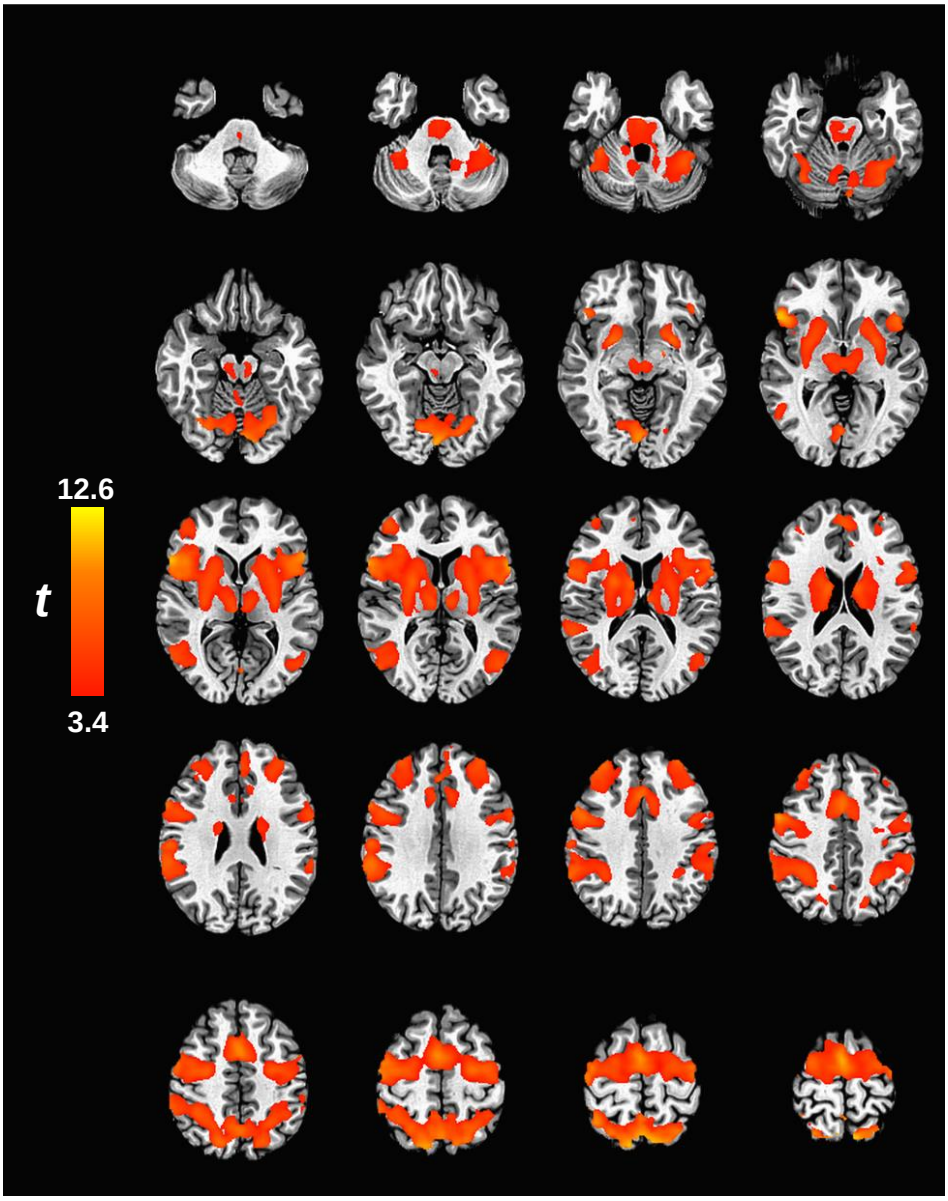


*Figure 27*. Axial view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the incentive-modulated antisaccade task during the rested baseline sleep condition (n = 12). Only clusters with at least 109 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at z = -35 (ventral) and progress in increments of 5 voxels to z = 60 (dorsal) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 8.

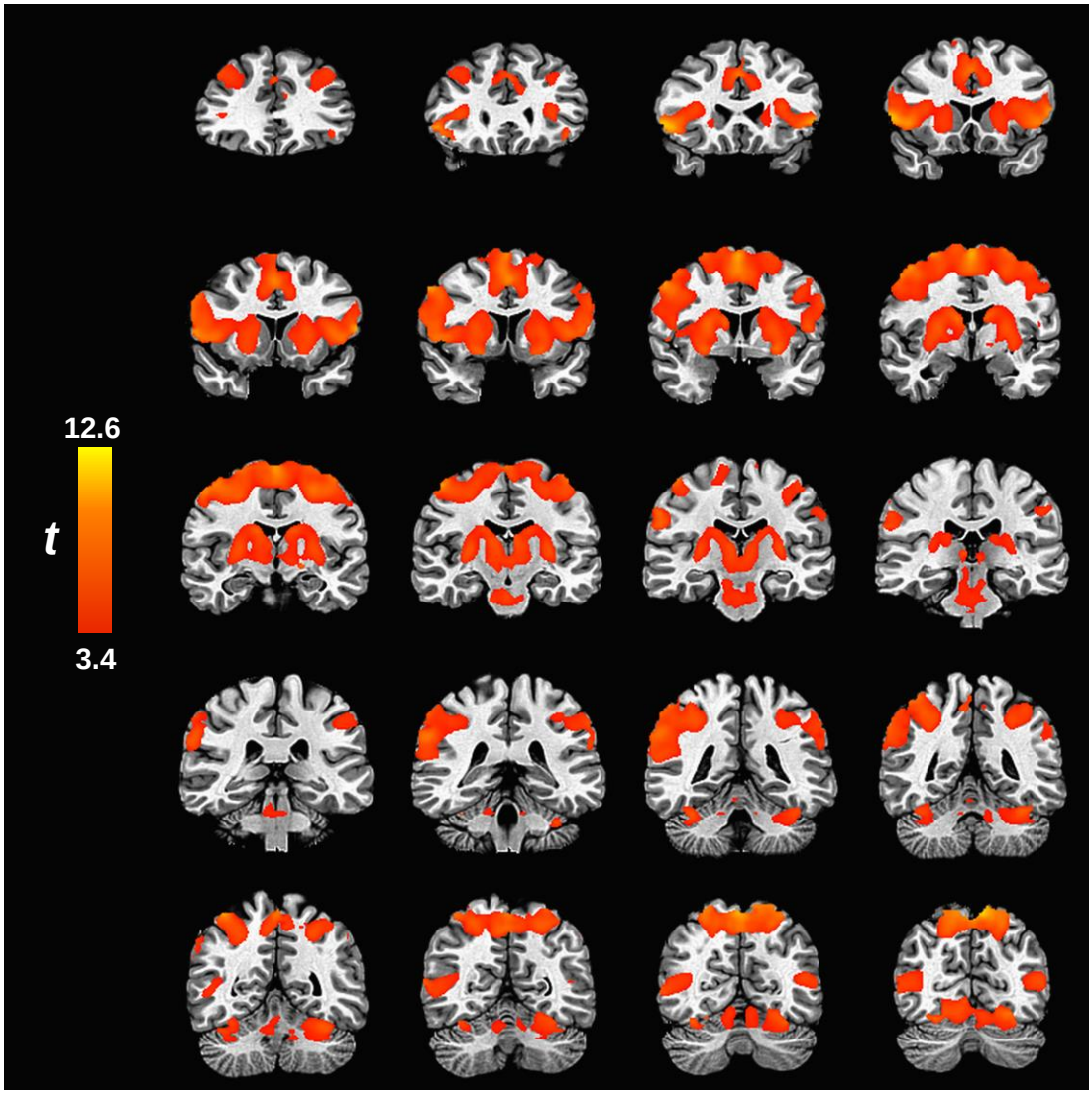


*Figure 28*. Coronal view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the incentive-modulated antisaccade task during the rested baseline sleep condition (n = 12). Only clusters with at least 109 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at y = 30 (anterior) and progress in increments of 5 voxels to y = -65 (posterior) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 8.

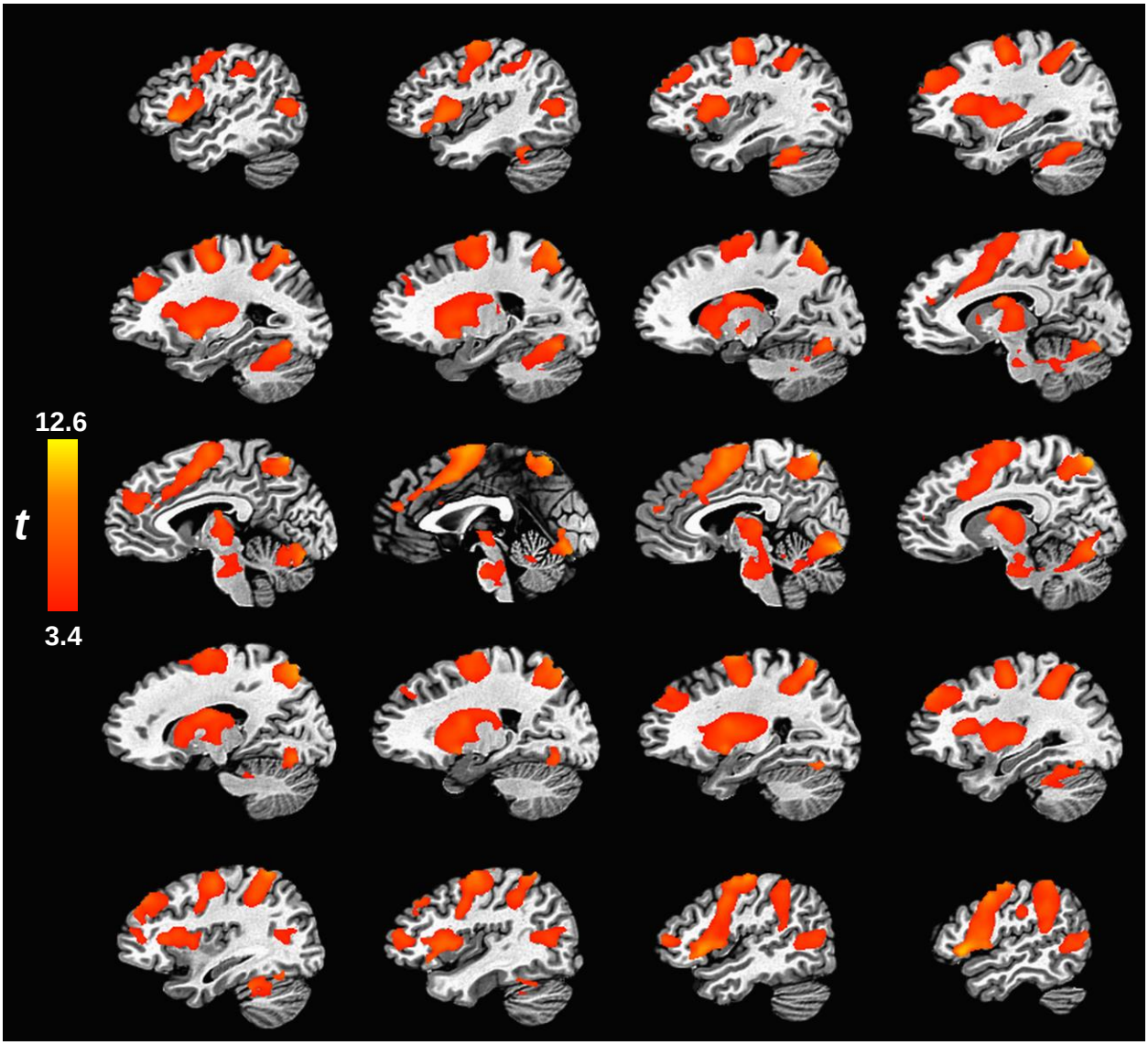


*Figure 29*. Sagittal view of whole-brain activation corrected for FWE (family-wise alpha = 0.05) on the incentive-modulated antisaccade task during the rested baseline sleep condition (n = 12). Only clusters with at least 109 contiguous voxels survived correction at a voxel-wise p threshold of 0.001. From left to right and top to bottom, slices begin at x = -45 (lateral left hemisphere) and progress in increments of 5 voxels to x = 50 (lateral right hemisphere) in the bottom-right corner (Talairach coordinates). Clusters and activation peaks are listed in Table 8.

### FMRI Power Calculation

FMRI data was used to conduct a *post hoc* power analysis, as described in Approach. The power analysis was conducted using the group map contrasting rewarded antisaccade > neutral antisaccade trials during sleep restriction > baseline on the incentive-modulated antisaccade task. This yielded a minimum sample size of 21 in order to achieve 80% statistical power.

## Balloon Analog Risk Task (BART)

### Task Description

The BART is a validated assessment of participants' propensity for risk-taking behavior (Lejuez et al., 2002; White, Lejuez, & de Wit, 2008). This task was administered to participants on a mobile tablet as part of a cognitive battery (Joggle Research App; Joggle Research, Seattle, WA) approximately every two hours of wake time during the inpatient stay (Figure 1). On the BART, participants were shown a balloon on the tablet screen and provided the option either to inflate the balloon or to collect a reward in exchange for the balloon. The reward-value for the balloon was proportional to the current size of the balloon. Each time the balloon was inflated, its size increased, and its associated reward-value increased by one increment. However, each inflation also increased the odds that the balloon may pop. If the balloon popped, then the reward could not be collected. The maximum number of inflations per balloon followed a randomized sequence of up to 9, 11, or 13 maximum pumps before popping. If the current balloon had a maximum number of 9 pumps before popping, then the probability of popping upon each inflation of the balloon followed a probability

distribution such that the first pump had a 1/9 chance of popping, the second pump had a 2/9 chance of popping, etc. In contrast with other versions of this task, all balloons were of the same color and reward-value, regardless of the balloon's popping probability distribution. Participants were allotted 30 balloons for the task, and the collected rewards accumulated over the course of all 30 balloons. No tangible rewards (e.g., money) were actually awarded to the participants based on their performance on the task. Participants were merely given positive feedback via the task application itself, which displayed a cumulative reward-value throughout the task, and at the end of each task administration, participants were also shown a plotted graph of their performance across multiple administrations of the task.

**Analysis**

Total number of inflations on balloons that did not pop (adjusted pumps) were calculated for each administration of the BART. Adjusted pumps for each administration were then analyzed in a mixed effects model with fixed effects of condition, day into condition, and the interaction between those two variables and with random effects of subject.

**Results**

Total adjusted pumps on the BART increased from an average of 69.8 ± 1.8 (Mean ± SEM) pumps in the rested baseline condition to 73.6 ± 1.3 pumps in the sleep restriction condition. The average slightly decreased to 72.4 ± 2.5 during recovery. Figure 30 shows the mean within-subject changes in total adjusted pumps on the BART across each day of the study. Total adjusted pumps were analyzed in a linear mixed effects model with fixed effects of condition and random effects of subject. This revealed

a significant effect of sleep restriction (Beta = 4.25, 95% CI = 1.74-6.77, Standard Error = 1.28, p = 0.001) on total adjusted pumps on the BART, which returned to baseline following two nights of recovery sleep (Beta = 3.64, 95% CI = -0.77 to 8.05, Standard Error = 2.25, p = 0.106). Adding day into condition and condition x day into condition to the model only improved the conditional $R^2$ from 0.103 to 0.105. The conditional $R^2$ statistic is a goodness-of-fit measure that reflects the proportion of variance explained by both fixed and random factors in mixed effects models, and it is recommended above other $R^2$ statistics when assessing linear mixed effects models (Nakagawa & Schielzeth, 2013). Because adding fixed effects of day into condition and condition x day into condition to the model failed to improve the conditional $R^2$ by even a single percentage point, the addition of these terms to the model would be unwarranted. As a *post hoc* analysis, a Pearson correlation analysis found that total adjusted pumps, summed across BARTs on the same day as the sleep restriction fMRI scan, were correlated with neither the same-day difference in ventral striatal reactivity to reward trials versus neutral trials on the antisaccade task (Pearson's r = 0.130, p = 0.688) nor with the change in this difference relative to baseline sleep (Pearson's r = 0.013, p = 0.968).

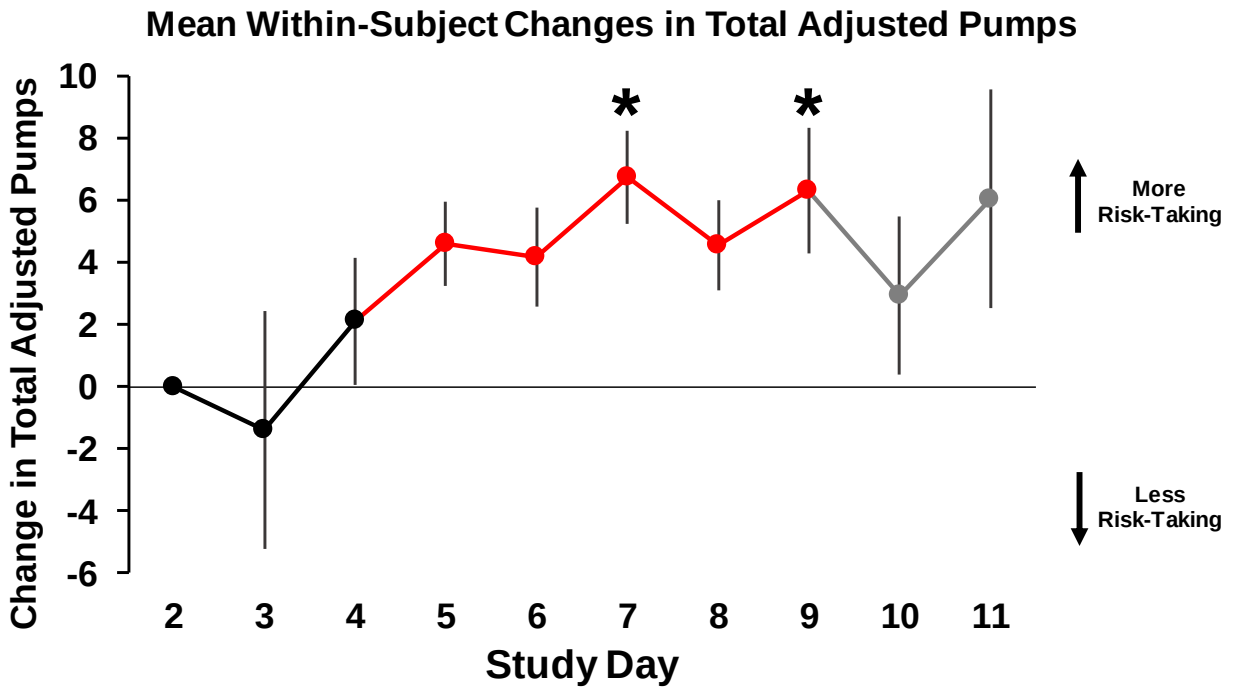


Figure 30. Mean (± SEM) within-subject changes in total adjusted pumps on the BART (n = 15). Changes during baseline (black), sleep restriction (red), and recovery (gray) are shown relative to the second day of the study. Positive changes correspond to increases in risk-taking, and negative changes correspond to decreases in risk-taking. In paired t-tests, mean within-subject changes on days 7 and 9 are significantly different from the last day of baseline ($p < 0.05$).

# Chapter 6. Discussion

## Interpreting Findings

This study sought to test whether partial sleep restriction to five hours in bed per night for five nights could induce changes in cognitive and affective functioning that had previously been reported following total sleep deprivation. After four nights of partial sleep restriction, three behavioral paradigms were administered in a fMRI scanner. Outside the scanner, participants completed a risk-taking task approximately every two hours of the study, as well as an appetite questionnaire before meals. It was hypothesized that sleep restriction under these conditions would have similar effects as had been observed with total sleep deprivation. Behaviorally, these hypotheses received mixed support. As expected, an established measure of risk-taking behavior was shown to increase during sleep restriction, but contrary to expectations, participants became less sensitive to threatening facial expressions and conveyed a weaker desire for calorie-dense foods. Results from fMRI were limited by constraints of statistical power. With only two exceptions, this study failed to detect any of the hypothesized differences in brain activation following partial sleep restriction. The first exception was an increase in BOLD signal in the right ventral striatum on reward versus neutral antisaccade trials during sleep restriction. The other was a decrease in BOLD signal in the anterior cingulate while evaluating the desirability of food images. However, because of the pilot nature of this study, these results cannot rule-out the possibility that more of the hypothesized effects might be detected in a larger sample. In fact, the direction of change in BOLD signal across conditions was often consistent with the

hypothesized changes, and prior to correction for FWE, the right anterior cingulate showed the hypothesized reduction in activation on the food desirability task following sleep restriction in an area only a few voxels away from the predefined ROI.

**Increased Striatal Reactivity to Reward**

This study found that the difference in ventral striatal response during reward trials relative to neutral trials on the antisaccade task was greater after 4 nights of 5 h TIB than during a rested baseline. A review of the fMRI literature reveals that, consistent with the electrophysiology literature, the ventral striatum is consistently implicated in the anticipation of reward (Knutson & Cooper, 2005). The observation that the ventral striatum shows a greater response during reward trials than neutral trials on this particular task paradigm has previously been reported in the literature (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015). However, this is the first study to show that the difference in response on this task increases following sleep loss, such that the ventral striatum becomes even more responsive to reward. In this case, the reward simply entailed the addition of a green frame around the perimeter of the screen and, at the outset of the reward block, instructions that the participants' accuracy would "win points" in their favor on subsequent trials. No scores were actually provided to the participants; they were only told that their performance would be scored accordingly during the researchers' analyses. In contrast, previous studies examining changes in the ventral striatal response on this task have used reward contingencies of actual dollar amounts paid to the participants (Geier et al., 2010; Padmanabhan et al., 2011; Paulsen et al., 2015). While the reward contingency of the present study might seem weak in comparison, it should be noted this is not the first study to observe putatively

reward-related changes in striatal activation without monetary incentives following sleep loss (Gujar et al., 2011). This effect has been repeatedly shown in sleep deprivation studies with monetary incentives on other tasks as well (Lei et al., 2017; Mullin et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011).

**Explaining the amplified striatal reactivity.** Mechanistically, one reason sleep-restricted participants might show greater striatal reactivity to reward has to do with the effects of sleep loss on dopaminergic signaling more generally. Specifically, positron emission tomography (PET) scans of radiolabeled D2/D3 receptor antagonists in the human brain have found decreased D2 and D3 receptor availability in the striatum following sleep deprivation (Volkow et al., 2012; Volkow et al., 2009; Volkow et al., 2008). Although decreased D2 and D3 receptor availability could indicate elevated dopamine neurotransmission, microdialysis experiments in rats indicate this is more likely due to a reduction in postsynaptic D2 and D3 receptor density accompanying sleep loss (Volkow et al., 2012). The latter finding is consistent with research showing that adenosine signaling, which tends to increase as a function of homeostatic sleep need (Porkka-Heiskanen et al., 1997), promotes the internalization of D2 and D3 receptors in the striatum (Hillion et al., 2002). With regards to the present study's findings, this is significant because activation of D1 receptors, the remaining dopamine receptor subtype, may be able to account for most of the ventral striatal BOLD signal in fMRI studies (Knutson & Gibbs, 2007). Crucially, D2 agonism has been shown to attenuate increases in ventral striatal blood volume in rats (Y.-C. I. Chen, Choi, Andersen, Rosen, & Jenkins, 2005), and D3 antagonism further potentiates the increases in blood flow due to D1 agonism (Schwarz et al., 2004). Therefore, the

reductions in D2 and D3 receptor densities that accompany sleep loss may lead to increased receptivity of the D1 receptors and, consequently, elevated BOLD signal in the ventral striatum (Greer, Goldstein, Knutson, & Walker, 2016).

**Inconsistencies in the literature.** A few sleep studies have failed to observe increased striatal reactivity to reward in individuals with shorter habitual sleep or total sleep deprivation (Greer et al., 2016; Menz, Büchel, & Peters, 2012; Telzer et al., 2013). One possible explanation for this inconsistency has been offered by Greer et al. (2016). The striatum contains the highest concentration of dopamine transporter (DAT) anywhere in the brain (Ciliax et al., 1999). Moreover, studies have shown that carrying at least one DAT allele with nine tandem repeats of a particular nucleotide base pair sequence results in elevated DAT levels (Faraone, Spencer, Madras, Zhang-James, & Biederman, 2014) and greater phasic dopamine activity (Aarts et al., 2010; Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009) in humans. Individuals carrying such an allele are termed “9R carriers.” Motivated by these findings, Greer et al. (2016) genotyped participants based on their DAT alleles and had participants complete an incentive-modulated psychomotor task after either a night of restful sleep or a night of total sleep deprivation. Using fMRI, they showed that only the 9R carriers exhibited increased reactivity in the ventral striatum during the anticipation of monetary reward following sleep deprivation. Given these findings, it is possible that the current study may have oversampled 9R carriers.

### Increased Risk-Taking on the BART

In addition to elevated striatal responsiveness to reward on the antisaccade task, this study also observed increased risk-taking on the BART during sleep restriction.

Previous studies of BART performance following sleep loss have yielded mixed results. While several studies have reported that sleep loss either has no effect (Bagley, 2011; Brown, 2008; Killgore et al., 2011) or even reduces risk-taking on the BART (Acheson et al., 2007; Killgore, 2007; Killgore et al., 2008), others have found increased risk-taking on the BART following partial sleep restriction to an average of 3 h TIB for one night (Rossa et al., 2014) and following one night of total sleep deprivation (Lei et al., 2017). Increased risk-taking on the BART has also been associated with shorter habitual sleep in adolescents (Telzer et al., 2013).

**Effort discounting.** Building on research showing that effort discounting increases following total sleep deprivation (Libedinsky et al., 2013), Killgore (2015) has suggested the BART may be susceptible to effort discounting in a way that other risk-taking tasks are not, given that it requires greater effort to take greater risks on the BART. However, Killgore et al. have also shown that risk-taking on the BART, even if it does not increase after 51 h, may significantly increase following 75 h of total sleep deprivation (Killgore et al., 2011), suggesting there may be a threshold at which changes in reward processing or a growing desire for self-stimulation are able to overcome the effort discounting. It is possible that the current study's divergent findings might be because 5 nights of partial sleep restriction to 5 h TIB affect reward processing differently than total sleep deprivation, but a better explanation has been offered by Lei et al. (2017), who observed increased risk-taking on the BART after a single night of total sleep deprivation. Consistent with the present study, Lei et al. used a version of the BART on which the maximum number of inflations per balloon was significantly less than the maximum 128 inflations reported by other studies (e.g., Killgore, 2007). The

BART used by Lei et al. (2017) and Telzer et al. (2013) allowed up to 10 pumps per balloon, whereas the BART used in the current study allowed up to 9, 11, or 13 pumps per balloon. Although it still requires greater effort in order to take greater risks, this version of the BART requires comparatively far fewer button-presses in order to take equivalent risks as on versions of the task used by other researchers, thus potentially reducing participants' susceptibility to effort discounting.

**Possible neural mechanisms.** The incentive-modulated antisaccade task involves similar cognitive and affective processes as the BART, so changes in inhibitory control or reward processing brain networks on one might predict performance on the other. The only positive result from the incentive-modulated antisaccade task in the current study was the finding that the right ventral striatum exhibited increased BOLD signal on reward versus neutral antisaccade trials following sleep restriction as compared to the rested baseline condition. However, this change in striatal reactivity was not associated with risk-taking on the BART. Other neuroimaging sleep studies have suggested a variety of neural mechanisms that might explain increased risk-taking on the BART following sleep loss. Telzer et al. (2013) observed decreased recruitment of the right DLPFC and weaker coupling of the right DLPFC with the insula and ventral striatum in adolescents on the BART. Given that their study was on a sample of adolescents, it is notable that adolescents exhibit weaker recruitment of the DLPFC when compared to adults on other tests of risk-taking (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). This is consistent with literature showing that the DLPFC is an area involved in cognitive control and the last brain region to develop fully in the adolescent brain (Gogtay et al., 2004). In a sample of sleep-deprived adults performing the BART,

Lei et al. (2017) saw increased reactivity of the inferior frontal gyrus to risk, greater reactivity of the ventral striatum and thalamus to reward, and weaker coupling of the posterior cingulate and VMPFC. As already mentioned, greater striatal reactivity to reward following sleep loss has been documented in a number of studies (Gujar et al., 2011; Lei et al., 2017; Mullin et al., 2013; Venkatraman et al., 2007; Venkatraman et al., 2011), and this finding is further bolstered by results of the present study. The VMPFC has also been previously implicated in studies of risk-taking following total sleep deprivation (Menz et al., 2012; Mullin et al., 2013; Venkatraman et al., 2011). The VMPFC or medial OFC is generally thought to encode outcome reward and loss associations (Rangel, Camerer, & Montague, 2008), and patients with damage to this part of the brain tend to make riskier decisions (Bechara, Damasio, & Damasio, 2000), a behavioral effect that has been replicated on identical tests in sleep-deprived participants (Killgore et al., 2006).

**Reduced Preference for Calorie-Dense Foods**

It was hypothesized that, consistent with previous studies (Benedict et al., 2012; Fang et al., 2015; Greer et al., 2013; Spiegel et al., 2004; St-Onge et al., 2011; St-Onge et al., 2014), participants would exhibit a stronger preference for calorie-dense over calorie-sparse foods over the course of partial sleep restriction to 5 h TIB for 5 nights. On the contrary, participants in this study actually reported a greater preference for calorie-sparse over calorie-dense foods on every day of the study. Moreover, participants' preference for calorie-dense foods actually decreased during sleep restriction. At least one other study has similarly reported a diminished preference for calorie-dense foods, as measured by *ad libitum* food consumption, following one night

of total sleep deprivation (Fang et al., 2015). However, the effect was specific to starchy foods and was offset by an increased preference for calorie-dense fatty foods, such that participants consumed more calories overall. In contrast, the reduced desire for starchy foods in the current study was not statistically significant.

**Discrepancy across different assessments of appetite.** Notably, the decreased desire for calorie-dense foods was only seen in the preprandial questionnaire data. Although not statistically significant, a shift in the opposite direction was seen on the food desirability task, such that participants showed a non-significant increase in preference for calorie-dense over calorie-sparse foods. This internal discrepancy between results from the preprandial questionnaire and the food desirability task suggests a possible explanation for the present study's discrepancy with previous studies. Specifically, participants may be evaluating their options differently if shown an image of each food item and if promised that they will be given a highly desired food item as a reward, as was the case with the food desirability task. By comparison, the preprandial questionnaire merely asked participants to consider in the abstract whether they might like to eat generic categories of foods. While it is striking that these differences would produce such strongly divergent results on superficially similar measures, this may be sufficient to explain discrepancies with most other studies of sleep loss and appetite. All the previously mentioned studies, except one (Spiegel et al., 2004), elicited participants' food preferences either while showing the participants images of food choices (Benedict et al., 2012; Greer et al., 2013; Rihm et al., 2019) or via selection from a menu of *ad libitum* food choices (Fang et al., 2015; St-Onge et al., 2011; St-Onge et al., 2014). The only study that diverged from this pattern was unique

in that the participants, after having fasted overnight, received a continuous infusion of glucose as their sole source of calories on the day on which their food preferences were assessed (Spiegel et al., 2004).

**Differences with previous studies.** Another possible explanation for this study's failure to replicate the effects of total sleep deprivation in previous studies involves differences in study conditions. Previous studies that have used fMRI to evaluate the effects of sleep loss on appetite have typically provided participants with considerably fewer calories preceding their fMRI scan sessions. Most of these studies enforced overnight fasting prior to fMRI scan sessions (Rihm et al., 2019; St-Onge et al., 2012; St-Onge et al., 2014). Others have instead allowed only a light snack, such as a single piece of toast (Greer et al., 2013) or glass of milk (Benedict et al., 2012), within 45 minutes of the scan session in an effort to diminish confounding effects of hunger. Only one study has allowed participants to consume food *ad libitum* on the same day as a fMRI scan, but that study reported resting-state analyses (Fang et al., 2015). By contrast, the current study fed participants 1,234-2,061 calories across the breakfast and lunch preceding each fMRI scan (see Methods for further dietary information). Lunch was served at 12:00, giving participants time to finish eating within two hours of the subsequent scan session at 14:30. This 14:30 scan session time was another defining feature of the present study. All the aforementioned studies conducted their scan sessions in the mornings (Benedict et al., 2012; Fang et al., 2015; Greer et al., 2013; Rihm et al., 2019; St-Onge et al., 2012; St-Onge et al., 2014). For those studies that restricted participants' caloric intake, a morning scan session time allowed for a prolonged period of calorie restriction that began after dinner and lasted until the scan

session in the morning. By itself, the lack of a comparable period of prolonged calorie restriction in the current study may be sufficient to explain the null fMRI results. Even when the effects reported in previous studies are adjusted for subjective hunger ratings, it is possible that a physiologic need for calories, rather than sleep loss or subjective hunger, may be driving the observed changes in hedonic valuation-related brain function. While this might account for differences in fMRI results, it should be noted that this would not, however, account for behavioral differences. Studies with *ad libitum* food access (Fang et al., 2015) or continuous glucose infusion (Spiegel et al., 2004) have reported a similar calorie-dense food bias as has been observed in fMRI studies with periods of fasting, yet the present study observed no significant calorie-dense food bias on either the preprandial questionnaires or the food desirability task.

**Possible change in hedonic valuation of the anterior cingulate.** Consistent with findings reported by Greer et al. (2013), this study found significantly reduced activation in part of the right ACC following sleep restriction compared to the rested baseline condition, prior to correcting for multiple comparisons. Specifically, the change in BOLD signal was seen in the 1-4 modulated functional map, which included an additional regressor for participants' valuation of food items on a 4-point scale from "strongly do not want" to "strongly want." This was the same modulation scheme used by Greer et al. (2013), who previously reported reduced activation in the right ACC on the same food desirability task following one night of total sleep deprivation. In addition to the 1-4 modulation scheme, the present study also tested an alternate 1-2 modulation scheme separately applied to "wanted" and "not wanted" food items. The rationale for this alternate modulation scheme was that the 1-4 modulation scheme does not

distinguish between brain regions involved in appetitive desire versus disgust, the latter of which might be elicited if participants reported they “strongly do not want” a food item. In fact, a meta-analysis of neuroimaging studies on disgust has identified the right ACC and bilateral insula, two of the ROIs reported by Greer et al. (2013), as two regions particularly involved in the experience of disgust (Vytal & Hamann, 2010). Although the 1-2 modulated maps should be more sensitive to regions that respond selectively to appetizing versus disgusting stimuli, this alternative modulation scheme did not reveal the same reduction in anterior cingulate activation following sleep restriction. Therefore, it is possible that the ACC might be less reactive to both appetizing and disgusting stimuli following sleep loss, and by collapsing across both types of responses, it might be easier to detect changes in ACC responsiveness, even when preferentially weighting appetizing stimuli (modulated 3-4) over disgusting stimuli (modulated 1-2) in the 1-4 modulation scheme. A reduced ability to recognize disgust in other people’s faces has been observed in participants reporting shorter habitual sleep (Holding et al., 2017) and has been observed in a dose-dependent matter over the course of total sleep deprivation (Ginani et al., 2017), but to this author’s knowledge, no sleep study has yet examined the experience of disgust directly.

**Reduced Sensitivity to Threatening Faces**

Lastly, this study found that participants were less likely to judge faces as threatening following 4 nights of sleep restriction to 5 h TIB when compared to a rested baseline condition. This was the opposite of what was expected. Using an identical social threat discrimination task, Goldstein-Piekarski et al. (2015) showed that participants were more, not less, likely to judge faces as threatening following one night

of total sleep deprivation. For comparison, Goldstein-Piekarski et al. (2015) reported that participants rated an average of 16.8 ± 7.8 (Mean ± SD) stimuli as “threatening” in the baseline condition, and this number increased to 20.4 ± 7.0 stimuli in the total sleep deprivation condition. The current study found that participants rated an average of 27.9 ± 4.9 (Mean ± SD) stimuli as “threatening” in the baseline condition, and this number decreased to 22.4 ± 4.1 stimuli in the sleep restriction condition. These appear to be comparable effect sizes but in opposite directions.

**Possible anchoring bias.** It is possible that the effect observed in the current study is merely due to habituation to the task. Although it is not clear precisely how Goldstein-Piekarski et al. (2015) explained the task to participants, it is possible that participants in the current study were cognitively anchored so as to expect a greater number of “threatening” faces. During the orientation to fMRI procedures before the first scan session, participants were briefly flashed a miniature spectrum of computer-generated faces, with one end of the continuum labeled “not threatening” and the other end labeled “threatening,” and participants were told that all faces on the task itself would fall along a similar spectrum (see Methods). For this reason, participants in the current study may have had greater insight into the construction of the task than participants in the study by Goldstein-Piekarski et al. (2015). Although the participants were not told anything that would approximately anchor their responses to an average of 27.9 out of 70 “threatening” stimuli at baseline or 22.4 out of 70 “threatening” stimuli during sleep restriction, it is possible that participants were expecting a larger share of “threatening” faces than they would have expected if they had not been provided with this information. Notably, the number of faces rated “threatening” was very similar

across the two studies' sleep loss conditions. Therefore, it is possible that participants in the current study were anchored to expect more "threatening" faces during the baseline condition but, after habituating to the task, converged on the same number of "threatening" faces as participants in the study by Goldstein-Piekarski et al. (2015). The order of conditions was counterbalanced across participants in the study by Goldstein-Piekarski et al. (2015), thereby controlling for these confounding effects of habituation. Arguing against this interpretation, however, the proportion of "threatening" ratings during the recovery sleep condition was significantly greater than the proportion during the sleep restriction condition. This would be more consistent with the interpretation that sleep restriction itself, not habituation to the task, reduced participants' sensitivity to threatening faces and that this sensitivity returned to baseline after a night of recovery sleep.

**Semi-chronic sleep restriction versus acute sleep deprivation.** A better explanation for these divergent results may lie in differences between the semi-chronic sleep restriction protocol of the current study and the acute sleep deprivation protocol by Goldstein-Piekarski et al. (2015). First, the comparison baseline conditions in each of these studies are not equivalent. In the study by Goldstein-Piekarski et al., participants received approximately 8 h TIB for one inpatient night during the rested baseline condition. In contrast, this study gave participants 10 h TIB for three inpatient nights during the rested baseline condition. Before the inpatient portion of this study, participants also were instructed to lie in bed and try to sleep for 10 h each night for 7 nights immediately preceding inpatient admission, which was confirmed via outpatient wrist actigraphy. The study by Goldstein-Piekarski et al. also monitored participants'

sleep habits preceding the study and found that participants' habitual sleep averaged approximately 7.5 h, but that study did not include a sleep extension element comparable to the present study. A second important difference between these studies is that a semi-chronic sleep restriction protocol like the one used in the current study is more susceptible to selection effects. Most notably, the present research was part of a larger collaborative effort that involved numerous blood draws, adipose biopsies, standardized meals, stool and urine samples, and hourly saliva samples across the 11-day inpatient protocol. Given the psychological demands of a study like this, volunteers were also required to complete a clinical psychological exam in order to be eligible for participation. These factors may select for participants that are unlike those in the sample studied by Goldstein-Piekarski et al. (2015). In particular, participants in this study may react differently to threatening stimuli or other stressors.

**Proposed brain mechanisms.** Given that the current study failed to identify any differences in brain function on the social threat discrimination across study conditions, it is difficult to speculate what sort of neural mechanism might account for a reduced sensitivity to threatening faces. In fact, no other study to date as yet examined sleep loss and emotional face recognition using fMRI except for Goldstein-Piekarski et al. (2015) and Motomura et al. (2013). Motomura et al. instructed participants to lie passively in the scanner while viewing happy, fearful, and neutral faces. There were no behavioral ratings of the faces in their study, but they showed that the left amygdala was more reactive to fearful faces after 5 nights of 4 h TIB as compared to a rested condition. Moreover, the increase in left amygdala reactivity was associated with decreased functional connectivity between the left amygdala and the ventral ACC. This

is potentially significant because previous literature has suggested that functional connectivity between the amygdala and part of the VMPFC near the ventral ACC may be predictive of anxious mood states (Murray, 2007). On studies specifically of emotional face recognition, the amygdala has repeatedly been shown to play a role specifically in the perception of threat-laden stimuli, including both fearful and angry faces (Vuilleumier, 2005). Therefore, it is possible that the decreased functional connectivity between the left amygdala and ventral ACC reported by Motomura et al. (2013) might lead to reduced sensitivity to threat-laden stimuli such as the angry "threatening" faces in the current study. Despite their divergent behavioral results, this interpretation would also be consistent with the fMRI results reported by Goldstein-Piekarski et al. (2015). Specifically, Goldstein-Piekarski et al. observed decreased coupling between BOLD signal in the amygdala and peripheral cardiac arousal, measured via heart rate. Notably, it has been argued that the VMPFC may play a central role in integrating peripheral emotional states, such as cardiac arousal, with higher-order cognitive processes (Bechara et al., 2000; Damasio, 1996). Although Goldstein-Piekarski et al. (2015) did not report decreased activation or coupling with the VMPFC, it is possible that the reduced amygdala-cardiac arousal coupling might be due to deficits in the same brain network. Killgore et al. (2006) has similarly argued that sleep deprivation might disrupt emotional integration in the VMPFC, given that sleep-deprived participants perform similarly on the IGT as patients with lesions in the VMPFC.

## Limitations & Future Directions

**Lack of female participants.** Due to the pilot nature of this study, it was not feasible to enroll an equal number of females to match the number of males in the study, while also controlling for differences in the ovulatory cycle. Since each inpatient portion of the study spanned 11 days, fluctuations in the ovulatory cycle could confound a variety of subjective and objective measures of sleep (Baker & Lee, 2018), in addition to possible confounding effects for the cognitive and behavioral domains of central interest to this study (Gorczyca et al., 2016; Iannello et al., 2015; Yamazaki & Tamura, 2017). The lack of female participants in the present sample means that the reported findings may not generalize. For instance, one study found that female participants did not report any change in appetite following sleep restriction (Omisade et al., 2010), contrasting with a previous study of similar design that included only male participants (Spiegel et al., 2004). The underrepresentation of female participants in human research is a well-known problem, compromising the scientific understanding of sleep and biological models of disease (Beery & Zucker, 2011; Driver et al., 1999). Future studies should investigate the effects of sleep loss on cognitive and affective functioning in gender-balanced samples.

**Small sample size.** Another significant limitation of this study is that it was underpowered due to its small sample size. This is certainly true at least for the social threat discrimination task, for which, unlike the other two fMRI tasks, data was made available for the exact same task administered following one night of total sleep deprivation (Goldstein-Piekarski et al., 2015). Using that data set, a power calculation was conducted using NeuroPowerTools (http://neuropowertools.org). Critical input

parameters for the analysis included: use of t-maps, screening threshold of p = 0.005, one-sample test, alpha = 0.05, smoothness estimates of 8 mm for X, Y, and Z dimensions, and a 3.0 $mm^3$ voxel size. Based on these parameters, a sample size of 54 participants was estimated to achieve at least 80% power. While such directly comparable data sets were never analyzed for the food desirability or antisaccade tasks, another NeuroPowerTools analysis of a food-related task suggested a sample size of 21 participants to achieve 80% power. In light of concerns about statistical power, the antisaccade task was adapted to a block design at the outset of the study specifically for the purposes of maximizing statistical power.

Null findings reported in the present study are difficult to interpret, given that this study may not have been sufficiently powered to detect the hypothesized effects in the first place. Conversely, positive findings are more likely to be type I errors. This is because the true probability that a research finding is indeed true depends not only on the post-study level of statistical significance but also the prior probability of a true finding and the statistical power of the study (Ioannidis, 2005). In other words, studies with weaker statistical power have a greater chance of yielding false positives and failing to replicate. Improving statistical power usually entails either recruiting more participants or increasing the number of task stimuli per study condition (Durnez et al., 2016). In the present case, the former was cost prohibitive, but an attempt was made in the latter vein by adapting the antisaccade task to a block design.

To help inform future study design, the *post hoc* power analysis found that a minimum sample size of 21 participants would be needed to achieve 80% statistical

power when replicating findings from the incentive-modulated antisaccade task in future studies.

**Order effects.** Because this study lacked either a control group or crossover design, any within-subject effects are confounded by order effects and effects of time-in-lab. For instance, it is difficult to distinguish the recovery condition from merely the condition during which the participant has been in-lab the longest. Potential effects of time-in-lab include those incurred by the controlled diet, sustained sedentary activity, a stabilizing bedtime, and habituation. As previously explained, habituation was of particular concern on the social threat discrimination task, which may have been confounded by an anchoring bias in advance of the first scan session. Future studies can account for these order effects by implementing a "washout" period of several weeks between baseline and restriction conditions, in combination with a counterbalanced crossover design. Moreover, the three fMRI tasks were always administered in the same sequence, confounding each task's effects with effects of time-into-sequence. Future studies can account for this problem by randomizing the order of tasks upon each administration.

**Task incentives.** Participant performance on the BART and incentive-modulated antisaccade task was only incentivized with the use of a "points" system, rather than a monetary reward. This was not the first study to report putatively reward-related changes in brain activity following sleep loss in the absence of a tangible reward (Gujar et al., 2011). Nevertheless, caution should be taken when interpreting or extrapolating from results on the BART and incentive-modulated antisaccade task in the present

study. Future studies should include performance-based monetary rewards on each of these tasks.

**Missing and noisy eye-tracking data.** Eye-tracking data from the current study showed that correct responses averaged 66 ± 4% (Mean ± SEM) on antisaccade trials and 70 ± 5% on prosaccade trials. Previous research involving healthy participants in the same age range observed 62 ± 3% correct responses on antisaccade trials and 92 ± 1% correct responses on prosaccade trials (Unsworth, Spillers, Brewer, & McMillan, 2011), while others have observed as high as 82 ± 12% correct responses on antisaccade trials (Luna, Garver, Urban, Lazar, & Sweeney, 2004). However, data from the current study was acquired via a remote optical eye-tracking device positioned several feet outside the fMRI scanner, which may not have been ideal. 18 of the 35 incentive-modulated antisaccade task sessions produced no usable eye-tracking data at all, and an average of only 62 out of 90 trials (69%) were valid on runs with any usable data. Possible sources of noise include the eye-tracking device's manual calibration process, as well as various kinds of optical interference (e.g., watery eyes, MRI-safe glasses on some participants). Noise might be greatly reduced in future studies with the use of a goggle system instead.

**Potential selection effects.** Because this 11-day protocol was particularly strenuous, especially when considering that various bodily fluids were collected and that abdominal fat was biopsied for other components of the study, applicants who were willing to participate in this study may not have been representative of the broader population. In fact, the region from which participants were recruited does not capture all the variance of a broader, national population. As already discussed, this study did

not even include any female participants. These are important caveats when considering the generalizability of the reported findings.

**Conclusions**

While these findings are tempered by a small sample size, partial sleep restriction to five hours in bed per night for four nights does not appear sufficient to produce or to detect changes in brain function that have been previously reported following one night of total sleep deprivation. There were only two exceptions. The first of these was an increase in BOLD signal in the right ventral striatum in response to reward versus neutral trials on an antisaccade task, which mirrored similar findings on other tasks in the sleep literature. Putatively reward-related increases in striatal reactivity may explain the well-known association between short sleep duration and substance use, as well as a variety of other risk-taking behaviors. Consistent with this interpretation, risk-taking behavior was shown to increase during the sleep-restricted condition. The second change in brain function was a reduction in BOLD signal observed in the anterior cingulate while participants evaluated food images. This finding is consistent with previous studies and may reflect a weaker reliance on deliberative processes when assessing food desirability. Despite consistent reports of an enhanced preference for calorie-dense foods in previous sleep restriction studies, this study found that, in the absence of food images or tangible food rewards, sleep-restricted participants actually report a reduced preference for calorie-dense foods. Moreover, this study did not find that sleep-restricted participants became more sensitive to threatening faces. On the contrary, sleep-restricted participants were less sensitive to threatening faces. This may be due to a diminished ability to integrate peripheral emotional cues, as

has been reported in previous studies. Future studies will be needed to replicate these findings in larger, statistically powered samples.

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Work on the molecular basis of bacterial keratitis
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## PUBLICATIONS

**Strayer, S. M.**, Lee, S., Nahmod, N. G., Master, L., Hale, L., Berger, L. M., & Buxton, O. M. (2019). Poor sleep health is associated with higher odds of alcohol use among adolescents. [under review]

Buxton, O. M., Nahmod, N. G., & **Strayer, S. M.** (2017). Studying sleep in family contexts via actigraphy and wearable devices. In S. M. McHale, V. King, & O. M. Buxton (Eds.), Family contexts of sleep and health across the life course. New York: Springer.