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The impacts of sleep and sleep deprivation on human brain and behavioral incentive processing

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Abstract

The impacts of sleep and sleep deprivation on human brain and behavioral incentive processing

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Professor Matthew P. Walker, Chair

Despite an emerging link between alterations in motivated behavior and a lack of sleep, the impact of sleep deprivation as well as the potential benefit of sleep, when it is achieved, on human brain mechanisms of reward and punishment remain largely unknown. Targeting these unanswered questions, this thesis aims to determine the impact sleep loss on human brain incentive processing in topics of 1) food desire and 2) monetary gains and losses. From these investigations four main findings have emerged that make up the first four chapters of this report: 1) In the context of food choices, sleep deprivation leads to significantly decreases activity in appetitive evaluation regions within the human frontal cortex and insular cortex during food desirability choices, combined with a converse amplification of activity within the amygdala ultimately leading to increased high calorie food choices. 2) In the context of monetary rewards and losses, sleep deprivation did not lead to measurable changes in activation to the anticipation of rewards and losses in the nucleus accumbens or insula respectively. However, sleep deprivation did lead to diminished medial prefrontal cortex responses to gain outcomes and increased anterior insula response to loss outcomes. 3) Although there were no observable sleep deprivation group effects on anticipation of monetary gains and losses, there was a significant interaction of sleep deprivation with a trait dopamine transporter genetic polymorphism that determined the impact of sleep deprivation on anticipatory response to gain and loss in the nucleus accumbens and anterior insula respectively. 4) In the context of learning from monetary incentives, sleep deprivation led to a specific deficit in the ability to learn from monetary gains but no change in the learning profile for monetary losses. Finally, in addition to these four findings on the impacts of sleep deprivation on human incentive processing, the final chapter (5) focuses on the relationship between sleep, when it is achieved, and next day reward responsivity. Here there is a significant relationship between individual

differences in REM sleep beta power and next day nucleus accumbens response to anticipation of rewards. Beyond these basic scientific insights, such results offer potential clinical relevance given that sleep disruption is highly co-morbid with numerous psychiatric and neurological conditions associated with dysfunctional dopaminergic reward processing (e.g., Parkinson's disease, substance abuse, and obesity). Such findings further indicate that sleep intervention may represent an under appreciated and novel therapeutic target particularly for disorders of the reward system.

Table of Contents

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I. Introduction

Sleep is vital to survival and common across a vast array of phylogeny (Allada and Siegel, 2008). We, as humans, spend nearly one-third of our time sleeping, yet our scientific understanding of the functions of sleep remains surprisingly limited. Initial speculation described sleep as an "inactive" state, or assumed that sleep had a singular function. However, discoveries over the past two decades have made clear that sleep serves a myriad of bodily and brain functions (Perogamvros and Schwartz, 2012, Abel et al., 2013, Goldstein and Walker, 2014), the latter including affective brain processing (Perogamvros and Schwartz, 2012, Goldstein and Walker, 2014).

To date, research examining the interaction between sleep and affective brain processing has predominantly focused on negative emotion, demonstrating that sleep deprivation leads to poor mood (Zohar et al., 2005) and increased neural sensitivity to negative emotional stimuli (Yoo et al., 2007, Prather et al., 2013). In contrast, relatively little attention has been paid to how sleep (and a lack thereof) influences positive affective processing and associated reward network functioning. The importance of addressing this knowledge gap, particularly for reward system processing, extends translationally, beyond the basic scientific merit, for at least three additional reasons: 1) professionally, in the context of circumstances where sleep loss and risk-taking co-occur (e.g. financial money markets), 2) within public health, especially in the context of vulnerable populations where risk-taking and insufficient sleep are common (e.g. obesity, adolescent youth), and 3) clinically, shedding light on disorders where sleep disruption and dysfunctional reward processing are co-morbid (including disorders of addiction, mood disruption and Parkinson's disease).

Building on these unanswered questions, this thesis aims to determine the impact of sleep and sleep loss on human brain incentive processing. Specifically the studies will examine 1) the influence of sleep deprivation on neural and behavioral food desire, 2) the influence of sleep deprivation on dissociable networks involved in gain and loss processing and their interactions with dopamine transporter genetics, 3) the affects of sleep deprivation on incentive reinforcement learning and 4) the relationship between sleep physiology and next day neural reactivity to reward anticipation.

The remaining introduction will provide context motivating these investigations. Beginning by offering initially separate overviews of sleep and reward brain processing, followed by a discussion of what is currently known about their interaction. The introduction will then conclude by stating the overarching thesis hypothesis and associated predictions.

Sleep

Sleep is a dynamic brain process that can be monitored in humans using Polysomnography (a method combining electroencephalogram (EEG), electroculargram (EOG) and electromyogram (EMG)) and characterized into two primary types: rapid-eye-movement (REM) sleep and non-rapid-eye-movement (NREM) sleep (Rechtschaffen and Kales, 1968). NREM sleep is further subdivided into four NREM sleep stages characterized by progressively slower frequency brain oscillations as well as changes in the presence of sleep spindles (short 1-1.5 sec bursts of sigma frequency activity). REM sleep is characterized by markedly faster EEG brain activity as well as atonic muscle activity and distinct fast eye movements (Rechtschaffen and Kales, 1968).

In addition to these electrically monitored sleep characterizations, there are also marked alterations in neurotransmitter levels as well as regionally specific brain glucose consumption that are dissociable between REM and NREM sleep states(Goldstein and Walker, 2014). Focusing here on REM sleep due to its association with affective processing, neuroimaging of REM sleep brain function reveals increased brain activity in affectively relevant brain areas including, amygdala, striatum, hippocampus, insula cortex and medial prefrontal cortex (Nofzinger, 2005, Miyauchi et al., 2009, Dang-Vu et al., 2010). REM sleep is also characterized by substantial reductions in noradrenaline/norepinephrine levels throughout the brain (Ouyang et al., 2004) and, as discussed below, dopamine levels are increased during REM sleep within the striatum and this action may be important for transitioning into REM sleep (Dahan et al., 2007).

The influence of sleep on waking neural activity can be studied in a variety of ways to uncover progressively more subtle affects of sleep function. One powerful manipulation is comparing the impact of total sleep deprivation, relative to a full night of sleep. This affords the ability to bi-directionally test the functional brain alterations caused by the absence of sleep, relative to the presence of sleep, and for the latter, help determine what type and physiological quality of sleep supports specific brain processes. This widely used method offers an important first line of evidence for establishing the involvement of sleep in specific processing domains.

Reward

The mesolimbic reward system governs a range of survival-motivated behaviors, including the ability to approach rewards and avoid punishments (Haber and Knutson, 2010, Perogamvros and Schwartz, 2012). Additionally, this system powerfully influences learning and memory, biasing the encoding of salient rewarding information and further contribute to the experience and recognition of positive emotions more generally (Haber and Knutson, 2010, Perogamvros and

Schwartz, 2012). At the same time, dysfunction of this system can lead to a wide range of deleterious and even life-threatening conditions including substance abuse, impulsive risk-taking, uncontrolled thrill seeking and has been recently linked to overeating behavior that causes obesity.

Central to these motivation functions are a network of dopaminergic governed brain centers. These including the mid-brain ventral tegmental nucleus (VTA) and substatia nigra that project most abundantly to the striatum in the basal ganglia, and specifically the nucleus accumbens (Haber and Knutson, 2010). Stimulation along this pathway leads to approach behavior and thus this system is widely considered to be the reward system or the seeking system (Ikemoto and Panksepp, 1999). In contrast, avoidance behaviors, can be elicited by stimulation of a separate pathway, descending from the anterior insula and basolateral amygdala through the stria terminalis to the periaquiductal grey (Panksepp, 1998). Furthermore, both systems are further connected to, and regulated by, areas of the frontal lobe that are important for integrating and guiding motivated action, as well as experiencing emotional feelings (Kringelbach, 2005, Wallis, 2007, Haber and Knutson, 2010).

The mesolimbic reward system is responsive to a variety of incentives including primary rewards (e.g. food and water) as well as secondary rewards (e.g. money and pleasurable visual stimuli). In human studies of reward processing, money is often used as an incentive stimulus because the value is easily manipulated and also because it can be both given (i.e. monetary gains) or taken away (i.e. monetary loss). Although evidence is still limited, studies have begun to investigate the altered response to these variable types of rewards under sleep deprivation. There is now clear evidence that the anatomical systems, and associated brain functions discussed here are sensitive to sleep; both its beneficial presence and detrimental absence. However, the specific dynamics of this interaction and the consequences of the sleep and incentive system interactions on human behavior are still under active investigation.

Sleep & Dopamine

Recent evidence is uncovering an important reciprocal relationship between dopamine regulation and sleep (Perogamvros and Schwartz, 2012). This neurochemical may represent one direct mechanism through which interactions between sleep/sleep loss and reward processing can be understood. Several lines of evidence offer tentative support.

Dopamine function has a significant governing influence on sleep. Levels of dopamine activity alter the timing of sleep through its wake promoting (hence sleep inhibiting) effects (Dahan et al., 2007). Interestingly, the wake-promoting action of stimulant drugs also appears to operate, in part, through blockade of

dopamine metabolism thereby increasing dopamine transmission(Qu et al., 2008, Andersen et al., 2010). Conversely, depleting catecholamines, which include dopamine, will induce sleepiness (McCann et al., 1993). However, once sleep is initiated, dopamine neurons influence the initiation and maintenance of REM sleep, increasing in their phasic firing just before REM sleep onset (Dahan et al., 2007). Furthermore, lesions to dopaminergic brain circuitry, including the midbrain and striatal regions, dysregulates REM sleep, which can manifest as increases or decreases, depending on the specific striatal area targeted (Qiu et al., 2010).

Not only does dopamine influence sleep, but reciprocally, sleep and a lack thereof regulates dopamine function. Human PET studies have shown that one night of total sleep deprivation down-regulates dopamine D2/D3 receptors within the striatum in humans (Volkow et al., 2008, Volkow et al., 2012). Moreover, the extent of indexed D2/D3 receptor down-regulation correlates with self-reported subjective sleepiness. This latter finding suggests that dopamine receptor decreases may be related to the severity of the sleep deprivation, at least in terms of subjective perception of tiredness. One explanatory hypothesis of these data relates to the chemical adenosine, which accumulates from energetic cellular processes with increasing time awake. The increased adenosine buildup, due sleep deprivation, may trigger the down-regulation of the D2 receptors by way of the adensosine A2a receptors, which, when activated, can drive D2 receptor internalization (Volkow et al., 2012).

Interestingly, reductions in D2/D3 receptors in the striatum are common across many substance use disorders (Volkow et al., 2007), as well as the condition of obesity (Volkow et al., 2011). Moreover, this functional change has been linked to the transfer from casual substance use to compulsive substance use (Volkow et al., 2007). However, it remains unclear what process(es) trigger these D2/D3 receptor reductions in these circumstances, with theories including genetic vulnerability, the drugs themselves, and environmental factors. Given the robust link between sleep deprivation and substance abuse disorders as well as obesity (Wong et al., 2004, Cappuccio et al., 2008, Berro et al., 2014), this sleep deprivation dependent reduction in D2/D3 receptors provides an intriguing candidate mechanism for how chronic D2/D3 reductions may emerge.

Sleep Deprivation & Reward

Building on this knowledge that sleep and dopaminergic reward systems actively interact, experiments in humans have further elucidate the neural and behavioral consequences of sleep deprivation on reward-related behavior. In this context, sleep deprivation in humans has been associated with an increase in high-risk gambling behavior, primarily when it comes to the possibility of uncertain financial gains (McKenna et al., 2007, Venkatraman et al., 2011). Complementing these

behavioral observations, neuroimaging findings have shown that sleep deprivation increases ventral striatum activation during mixed monetary gamble decisions, specifically for trials involving high risk (Venkatraman et al., 2007b, Mullin et al., 2013). However, it is relevant that studies have employed tasks that involve mix possible monetary gains and losses combined in each trial. Therefore, it currently remains unclear whether the profile of enhanced risk-taking caused by sleep deprivation arises from (1) a heightened sensitivity to gain, (2) a decreased sensitivity to loss, or (3) a combination of both. This is relevant since gain- and loss-processing are governed by at least partially discrete anatomical networks (Yacubian et al., 2006, Knutson and Greer, 2008). As a result, any disambiguation will require tasks that isolate gain and loss separately. Furthermore, pharmacological dopamine manipulations can lead to specific deficits in gain related learning independently of loss related learning (Pessiglione et al., 2006). Understanding these differential gain and loss biases will be important for predicting behavior under sleep deprivation as well as further understanding disorders that elicit systematic gain or loss processing biases.

Enhanced reward-sensitivity associated with insufficient sleep does not appear to be limited to monetary stimuli. Amplified reactivity within the striatum and amygdala following sleep deprivation has been observed in response to pleasurable emotional pictures. Moreover, these neural changes are associated with an increased behavioral tendency to rate neutral pictures as positive (Gujar et al., 2011b). Given that much of human daily reward-related decision-making is not restricted to money, it is relevant to elucidate if/how sleep-deprivation changes reward system functioning in response to non-monetary incentive stimuli. Food rewards provide a particularly interesting target considering 1) their status as a primary reward, 2) their ubiquity in daily life, and 3) their contribution to health and, conversely, obesity.

It is important to note that some reports have failed to show significant reward-brain group/condition differences caused by sleep deprivation, or only demonstrate effects on an individual subject level (Libedinsky et al., 2011, Libedinsky et al., 2013). Furthermore, studies do not commonly identify increases in impulsivity or impulsive behavior under conditions of sleep deprivation that might be expected given the changes in reward-approach behavior discussed above (Acheson et al., 2007, Libedinsky et al., 2013). Understanding individual differences (that could potentially mask group effects) in these studies will be an important target of future research. Perhaps most obvious are genetic inter-individual differences. Genetic variations in the serotonin system have already been shown to functionally interact with sleep deprivation, resulting in different therapeutic responses to sleep deprivation in bipolar-depression patients depending on genotype (Benedetti et al., 2007). Similar polymorphisms associated with the dopamine system may offer one explanatory cause of inter-

individual differences (and lack of overall group effects) in reward sensitivity caused by sleep deprivation.

Sleep & Reward Function

In contrast to detriments caused by sleep loss, emerging evidence indicates that the presence of sleep beneficially supports several affective reward brain functions. For example, greater amounts of sleep from night to night predict higher positive mood ratings the following day (de Wild-Hartmann et al., 2013). Moreover, a daytime nap increases positive ratings of affiliative (Happy) facial expression, particularly if the nap includes REM sleep (Gujar et al., 2011a). Sleep has also been demonstrated to play a role in reward-motivated memory processing, enhancing the offline consolidation of both procedural skill memory (Fischer and Born, 2009) as well as declarative memory(Oudiette et al., 2013). In the latter study, the amount of REM sleep predicted changes in incentive processing, an interaction that preferentially biased memory items of high-reward value (Oudiette et al., 2013). Taken together, these findings signal a role for sleep, and REM sleep in particular, that optimally guides the assignment of appropriate reward value to a range of affective experiences. As a consequence, the brain is better capable of modulating the degree of reward-related reactivity, and furthermore, selectively shape the selection and thus long-term memory retention of these waking events.

Hypotheses

Taken together this collection of findings leads to the overarching prediction that sleep deprivation will lead to dysregulation in the dopaminergic mesolimbic networks with consequences for 1) appetitive food choices, 2) monetary incentive gain and loss sensitivity, 3) ability to learn form monetary gian and loss feedback and 3) the restorative benefit of REM sleep on next day reward processing. Specifically, this report will test the following four experimental hypotheses across the five chapters:

Hypothesis 1: Sleep deprivation will lead to increases in subcortical sensitivity to desirable foods and/or a failure to recruit cortical regions necessary for properly evaluating food choices. Ultimately, this further predicts that this neural profile will lead to increased desire for high calorie foods. (**Chapter 1**)

Hypothesis 2: Sleep deprivation will lead to dissociable alterations in the mesolimbic responses to anticipation of gains and losses in the nucleus accumbens and anterior insula. Furthermore, these changes will depend on a sleep-deprivation interaction with dopamine functioning, tested using individual differences in dopamine transporter genetics (which influence synaptic dopamine). (**Chapters 2&3**)

Hypothesis 3: Sleep deprivation will lead to dissociable differences in the ability to learn from incentive based reinforcement feedback. Building on literature showing that blockade of dopamine D2 receptors leads to specific deficits in the ability to learn form monetary gain (but not loss) feedback, similarly, sleep deprived subjects are predicted to show a deficit in the ability to learn from gains relative to losses. (**Chapter 4**)

Hypothesis 4: The quantity and spectral quality of REM sleep will predict individual differences in next day neural reward processing across subjects, specifically determining the relationship between REM-dopamine-related theta and beta EEG activity and next-day striatal reward reactivity. (**Chapter 5**)

Chapter 1

The neural and behavioral impact of sleep deprivation on food desire

Introduction

Mounting epidemiological data implicates sleep loss as a risk factor for obesity in both children and adults worldwide (Cappuccio et al., 2008). Moreover, sleep deprivation alters appetite-regulating hormones and increases caloric intake (Brondel et al., 2010, Hanlon and Van Cauter, 2011). Given the continued decline in sleep duration in industrialized nations, mirrored by the steep rise in obesity in these same populations (Cappuccio et al., 2008), understanding the association between sleep loss and weight gain has become of paramount concern for global public health.

Despite such population-level as well as peripheral body evidence, the central brain mechanisms explaining the impact of sleep deprivation on appetitive food desire that can lead to weight-gain remain unknown. Discovering such sleep-dependent neural dysfunction may represent a critical component to understanding the link between sleep loss and obesity (Hanlon and Van Cauter, 2011). It would further contribute to a central nervous system explanation for the failure to appropriately regulate dietary intake and thus develop or maintain obesity under conditions of insufficient sleep. Finally, this information will also help uncover the general brain mechanisms that support (or fail to support) proper incentive based decision making under conditions of sleep deprivation. Using a food-desire task in combination with human functional MRI (fMRI), here we sought to characterize the impact of sleep loss on the brain mechanisms governing appetitive food desire.

The study focused *a priori* on a discrete set of well-characterized cortical and subcortical regions of interest (ROIs) known to be instrumental in appetitive desire and food stimulus evaluation (Tang et al., 2012). At the cortical level, the anterior insula cortex, lateral orbital frontal cortex and anterior cingulate cortex, all have well established roles in signaling stimulus value across contexts, including appetitive choices, and in integrating food features that govern preferences (e.g., the odor and flavor of food) (Small and Prescott, 2005, Hollmann et al., 2012). Moreover, disrupted functional activity within frontal cortex, including these anterior cortical regions, is widely considered to be one hallmark of sleep loss (Muzur et al., 2002). At the subcortical level, both the amygdala and the ventral striatum have been strongly implicated in governing the motivation to eat (Tang et al., 2012). The amygdala has consistently demonstrated responsivity to food stimuli, especially when the salience of food stimuli are high (van der Laan et al., 2011). Activity in the ventral striatum in response to foods accurately predicts immediate food intake (Lawrence et al., 2012), binge eating (Wang et al., 2011) as well as real world weight gain (Demos et al., 2012). Moreover, previous work has demonstrated that activity in the

amygdala and striatum in other (non-appetitive) affective tasks is elevated following sleep loss (Venkatraman et al., 2007a, Yoo et al., 2007).

Building on this established literature, the current study sought to test two non-mutually exclusive hypotheses regarding the central brain mechanisms that may lead to weight-promoting food choices following sleep loss: 1) failure to recruit cortical regions necessary for optimal evaluation of food stimuli (the anterior cingulate, the lateral orbitofrontal cortex and the anterior insula); a profile that could lead to improper food choice selection (i.e. choosing items with greater weight-gain potential), and 2) excessive reactivity in two subcortical regions known to signal food salience and promote eating behavior (the amygdala and the ventral striatum); a consequence of which may exaggerate food salience and motivated consumption for appetitive food stimuli, also leading to weight-gain potential. The findings reported here demonstrate not only reduced recruitment of all three key cortical regions necessary for food stimulus evaluation, but also amplified subcortical amygdala (yet not ventral striatal) reactivity under sleep deprivation. Such changes offer a novel explanatory brain mechanism by which insufficient sleep may lead to altered food choices and thus the development or maintenance of obesity.

Methods

Experiment Overview: twenty-three healthy participants (13 female; age: 20.5± 1.8 s.d.; body mass index: 23.0±1.8 s.d.) underwent a repeated measures, counterbalanced cross-over design involving a night of normal rested sleep (average 8.2 hr asleep) and a night of monitored total sleep deprivation (average 24.6 hr awake), separated by at least 7 days. Participants ate a controlled snack (see eating schedule procedures below) at 2:30am in the sleep deprivation condition that contained a calorie amount sufficient to alleviate increased energy demands estimated to be expended due to staying awake. Together with a standardized breakfast in both conditions in the morning, this eating schedule resulted in hunger ratings (measured on 100mm visual analog scale (Spiegel et al., 2004)) that did not differ statistically ($p=0.28$) between sleep deprived (47.7±25.53 s.d. mm) and rested conditions (39.7±24.0 s.d. mm) preceding the MRI scan sessions. During each fMRI session (scan time 9:29AM±49min s.d.) participants rated 80 different food items that varied in calorie content on a 1-4 rating scale, according to how much they wanted that item “right now” (**Fig 1.1**). fMRI BOLD signal was correlated with these 1-4 ratings on a trial-to-trial basis, resulting in neural activation maps expressly sensitive to increasing food-choice desire. After the scan, participants actually received one food item based on their ratings, enhancing ecological incentive context and potentially reducing demand characteristics. Therefore, using this task we simultaneously monitored behavioral food desire as well as identified brain areas underlying these appetitive decisions, modeled and hence sensitive to increasing food desire.

Sleep condition procedures: Participants completed two experimental sessions 1) a night of normal sleep in the lab monitored by PSG (See sleep recording procedures in section *IV. Common Methods*) and 2) a night of total sleep deprivation (See sleep deprivation procedures in section *IV. Common Methods*) monitored by lab personnel from 9pm and wrist actigraphy. Sessions were separated by a minimum of 7 days (average 10 days) and counter balanced in order across participants. Participants completed fMRI scanning sessions the morning after each experimental night, starting at 9:08 AM +- 45min (range: 8:05am to 10:39am) on the sleep deprivation day and 9:50 AM +- 45min (range: 8:17am to 11:00am) on the sleep rested day. To ensure that participants were well rested before each session, they kept a regular sleep schedule (7-9 hours time in bed between 10pm and 10am) for three days prior to each session, verified by daily sleep diaries and wrist actigraphy. Subjects attained 8.08±1.0 s.d. hours time in bed across the three nights proceeding the sleep deprivation and 8.07±1.0 s.d. hours preceding the sleep rested condition.

Eating schedule procedures: Participants ate according to their normal diet throughout enrollment. During the sleep deprivation night, participants were provided with a controlled snack from 2:30-3:00am. This consisted of calorie content sufficient to offset increased energy expenditure associated with one night of sleep loss over a 24 hr period (reported as 134±2.1 s.d. Cal) (Jung et al., 2011). The snack contained the following four items: Fig Newtons (200 Cal), Gold Fish crackers (130 Cal), Ritz peanut butter crackers (150 Cal) and an apple (95 Cal), resulting in a total of 575 Cal available. On average, participants ate an estimated 485.2 Cal, with the least amount of calories consumed being approximately 160 Cal; and this was the only participant who consumed less than 300 Cal. Note that these estimates are based on calories per serving reported on the packaging and the proportion of the serving eaten by the participants (reported as none, half or all of the item). In addition, and in both sessions, all participants were given, and consumed, a small breakfast (one piece of toast with strawberry jam) approximately forty-five minutes before their scan session. Participants were monitored throughout both sessions to ensure that they did not eat anything in addition to this provided food (although water was not restricted). Self reported hunger levels (assessed on a 100 mm visual analog scale (Spiegel et al., 2004)) immediately preceding the scan session were no different between the rested and deprived conditions ($p=0.28$; also reported in Results). Both groups showed an increase in hunger levels compared to their study arrival baseline (**Fig 1.2**); important considering previous studies have shown that brain reactivity to food stimuli can be enhanced by subjective hunger (Siep et al., 2009).

Food Desire Task: In the food desire task, participants saw 80 food items and rated them on a 1-4 scale according to how much they wanted that food right now (details provided in **Fig 1.1**). In order to control for lateralized motor effects,

approximately half of the participants used their left hand to rate wanted items (1-strongly want; 2-somewhat want; 3-somewhat do not want; 4-strongly do not want) and the other half used their right hand (scale reversed). For all analyses, ratings were re-coded so that higher ratings indicated higher wanting. Participants were not informed of the hypotheses of the study nor were they told that they would be seeing foods that experimentally varied in terms of calorie content or food types that could otherwise establish preconceived biases.

In the task instructions, participants were informed that two food items would be revealed at the end of the scan, and a serving of whichever item they had rated as wanting more would be given to them to eat (which was carried out). They were further instructed that this meant it was in their best interest to rate each food item according to how much they actually wanted that item at the time of the session. This procedure was used to encourage participants to rate the food items according to their actual preferences (rather than according to experimental expectations or demand characteristics), and to ensure incentive compatibility in the task as in previous studies (Hare et al., 2009).

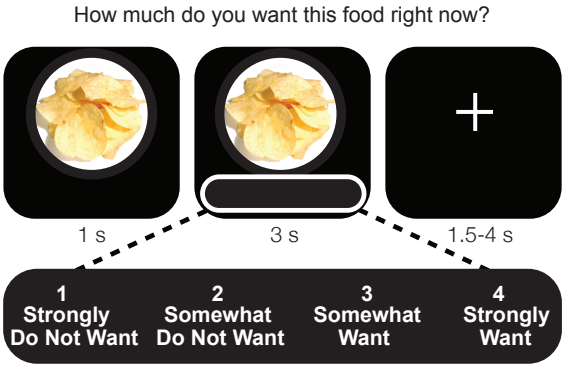

Fig 1.1) Food desire task trial structure. Participants saw and rated 80 food items on a scale from 1-4 according to how much they wanted the food item at that moment under sleep rested and sleep deprived conditions.

Stimuli: The task used 80 pictures of food with no packaging collected from internet searches and cropped to standardized circles. The items were evenly distributed across five categories (salty, sweet, starchy, fruit or dairy) and varied in calorie content (Range: 7.2 – 523.4; Mean: 139.8± 94.8 s.d. Cal per serving based on USDA database listings (ndb.nal.usda.gov)). The same 80 food items but a different picture of each item was used in each experimental session.

fMRI General Linear model: See fMRI scanning acquisition and preprocessing sections in *IV. Common Methods* for details on these methods. A separate general linear model was constructed for each subject which included 1) all trial onsets convolved with a canonical hemodynamic response function with a 3 second duration 2) A parametric regressor of the individual want ratings (1-4) for each food item convolved with a canonical hemodynamic response function with a 3 second duration (this was the regressor of interest) 3) The six movement-related covariates (three rigid-body translations and three rotations determined from the realignment preprocessing step). Separate regressors were used within the same model for each of the 2 scanner acquisition runs.

ROI Analysis: Guided by suggested ROI reporting policies (Poldrack, 2007, Poldrack and Mumford, 2009), regions of interests were taken as the average parameter estimates from 5 mm spheres centered around coordinates form previous literature examining food evaluation for the three cortical regions of interest as well as the amygdala, and reward responsivity for the ventral striatum. MNI Coordinates [x, y, z] were: amygdala (18, -12, -22) (van der Laan et al., 2011); ventral striatum (-12, 12, -10) (Knutson et al., 2008); Anterior cingulated cortex (15, 6, 38) (Small et al., 2003); Lateral orbital frontal cortex (-36, 42, -10) (Beaver et al., 2006); and bilateral anterior insula (-31, 22, 11 & 36, 17, 0) (Small et al., 1999).

Behavioral comparisons: Behavioral comparisons between rested and deprived conditions were carried out using paired t-tests. Correlation analysis was used for results in **Fig 1.4B**. Spearman's correlation analysis was used to investigate the relationship between calories across food items with the mean change in desire ratings across items.

Results

Neural responses to food desire under sleep deprivation: Compared to the sleep rested state, sleep deprivation significantly reduced activity in all three cortical regions of interest —the anterior cingulate cortex (T=3.87; p=0.0008), lateral orbital frontal cortex (T=2.08; p=0.0491) and anterior insula cortex (T=2.63; p=0.0154) —as food desire progressively increased (**Fig 1.3A**) confirmed by t-tests of averaged parameter estimates at 5mm spheres placed around literature based sites (see **Methods**). Note that this significance threshold is $p<$ 0.05 for each region, however, if all five regions of interest are considered as a family of independent tests and correcting for multiple tests we find that lateral orbital frontal cortex and anterior insula no longer survive this more stringent statistical threshold while the anterior cingulate remains significant. It should be noted that this approach makes an assumption of independence of these regions, which

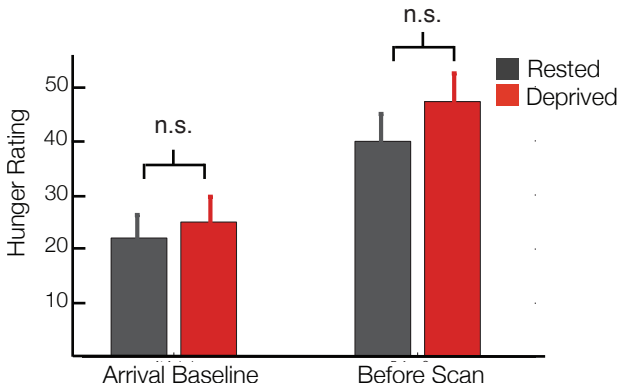

Fig 1.2) Self reported hunger levels. Collected using a visual analog scale with a 10cm line, y-axis is in millimeters. There were no significant differences between sleep rested and sleep deprived sessions either at arrival or before the scan session. However, hunger levels were significantly greater before the scan compared to arrival in both groups ($p < .05$; paired t-tests across 23 participants; error bars show standard error).

may not be the case considering their collective function in appetitive processing. When considering the subcortical regions of interest, the amygdala responsivity to the desirability of food items was significantly increased (T=3.08; p=0.0055) following sleep deprivation, compared to the sleep rested state (**Fig 1.3B**). In contrast, this profile of amplified subcortical activity was not observed in ventral striatum (T=-0.28; p=0.7852), showing no significant difference in responsivity between the sleep deprivation and rested conditions. Here again the amygdala survives correction for five comparisons if these regions are taken as a family of independent tests. Additionally, all ROIs demonstrating significance when comparing the average activity described above also express clusters of significant activity within these ROIs that survive familywise error (FWE) rate correction for multiple comparisons (p<0.05; **Table 1.2**). Taken together, these findings indicate that sleep deprivation diminished activity in an established set of cortical appetitive evaluation regions as food desire progressively increased, yet triggered a converse increase in subcortical amygdala reactivity known to signal food salience in the context of appetitive choice (van der Laan et al., 2011).

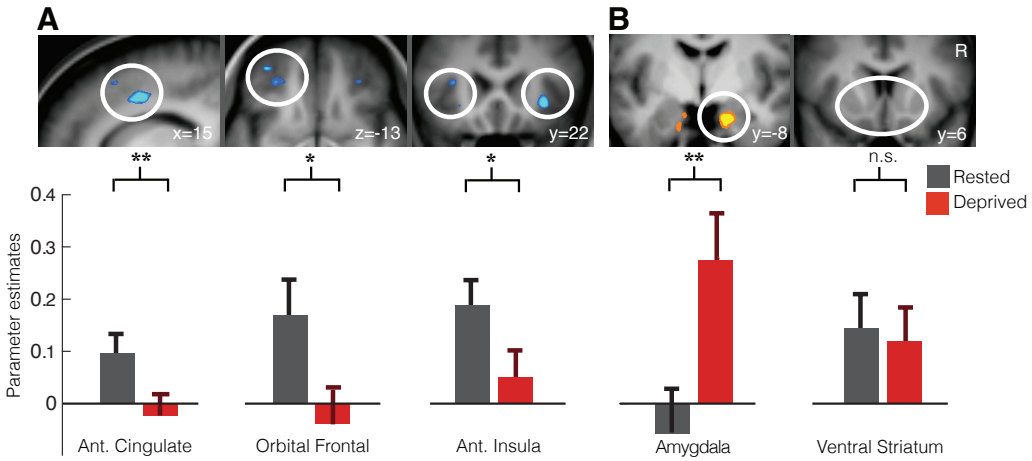

Fig 1.3) **Neural consequences of sleep deprivation on food desirability.** Sleep deprivation led to marked decreases in the anterior cingulate, left lateral orbital frontal cortex and anterior insula reactivity to food desirability (**A**). In addition, sleep deprivation led to a significant increase in amygdala reactivity to food desirability but no significant difference in ventral striatum reactivity (**B**). All parameter estimates are from a GLM with a parametric contrast of individual "want" ratings from twenty-three participants. Whole brain analysis (above) thresholded at p<0.005 for display purposes for sleep deprivation increases (**B**) and decreases (**A**). Region of interest analysis (below) are mean parameter estimates with standard errors of the mean extracted from 5mm spheres centered at foci taken form previous literature (See methods; circles indicate general areas of interest not specific foci; * indicates p<0.05 uncorrected for paired t-tests across 23 participants and ** indicates p<0.05 with Bonferroni correction for five regions of interest; error bars show standard error).

Table 1.1) Exploratory whole brain analysis

Region	T	Cluster Size	X	Y	Z
Sleep Rested > Sleep Deprived					
* L Putamen	4.99	104	-16	4	0
* L Hippocampus	4.00		-14	-10	-8
* R Thalamus	4.46	42	4	-10	-2
*** R Cingulate**	**4.37**	**24**	**16**	**2**	**40**
*** R Insula**	**4.22**	**20**	**32**	**24**	**-4**
* L Superior Parietal	4.21	25	-30	-68	52
L Parahippocampus	4.18	4	-20	-32	-8
* L Middle Frontal	3.91	17	-34	30	54
L Thalamus	3.84	8	-6	-18	-8
L Middle Frontal	3.72	2	-36	38	46
L Superior Frontal	3.69	9	-22	32	50
L Orbital Frontal	**3.65**	**1**	**-34**	**48**	**-14**
R Postcentral gyrus	3.58	7	32	-28	42
R Precuneus	3.51	1	18	-64	30
Sleep Deprived > Sleep Rested					
*** R Parahippocampus/Amygdala**	**4.39**	**29**	**18**	**-8**	**-26**
* R Inferior temporal lobe	4.11	30	48	-48	-18
R Supperior temporal pole	3.84	5	32	28	-24
L Fusiform	3.69	3	-30	-22	-28
L Cerebellum	3.69	7	-14	-72	-38
L Inferior temporal lobe	3.68	6	-56	-64	-22
L Inferior temporal lobe	3.60	3	-50	-56	-24
R Cerebellum	3.55	1	58	-50	-32
R Parahippocampal gryrus	3.55	2	28	-22	-32
R Superior temporal pole	3.54	1	52	20	-14

Exploratory whole brain analysis showing all peak activations (MNI coordinates) significant at $p<0.001$ (no cluster criteria) for paired comparison (Sleep Rested < > Sleep Deprived) of the parametric contrast of want ratings (i.e. regions correlated with increasing food desire and differing by condition). Bold indicates a priori regions of interest. Cluster size is in voxels; voxel size is 2 mm^3. Regions marked with * survive cluster correction criteria of ten voxels.

Importantly, self reported hunger levels were no different between the sleep rested and sleep deprived conditions (p=0.28; see **Fig 1.2**), indicating that differences in brain activity could not be explained on the basis of hunger differences alone.

Behavioral changes in food desire under sleep deprivation: Complimenting these changes in brain responsivity, we further examined whether sleep deprivation triggered an increased desirability for food items that carried the greatest weight-gain promoting potential i.e. high-calorie food items. Relative to the sleep rested state, sleep deprivation resulted in a significant increase in the proportion of "wanted" food items carrying high-caloric content (*T=2.21, p=0.04*). In contrast, no corresponding differences between the sleep rested and deprived states were observed for low calorie items (*T=1.15, p=0.26*; **Fig 1.4A**). Indeed, the total calorie content of all wanted items (summed together) in the sleep-deprived condition was significantly greater compared to sleep rested state (*T=2.07, p=0.05*), representing an additional 600 ±289 s.d. Cal average increase. Additionally, the level of caloric content across food items significantly predicted the extent to which desirability ratings increased after sleep deprivation; such that the highest calorie foods accrued the largest increase in desirability ratings following sleep deprivation (*Spearman's r=0.23, p=0.04*). Further implicating an association with insufficient sleep, increasing perceived severity of sleep deprivation across individuals, indexed by self-reported subjective sleepiness (Hoddes et al., 1973), was positively and significantly correlated with the percentage of wanted high-calorie foods (**Fig 1.4B**), and this correlation remained significant when controlling for body mass index using linear regression (T=3.41, p=0.003). Confirming the specificity of this finding to the state of sleep deprivation, no such association between subjective sleepiness and percentage of wanted high-calorie foods was observed in the sleep rested state (r=0.19; p=0.39). Additionally, body mass index was not correlated with the percentage of high calorie choices in either the

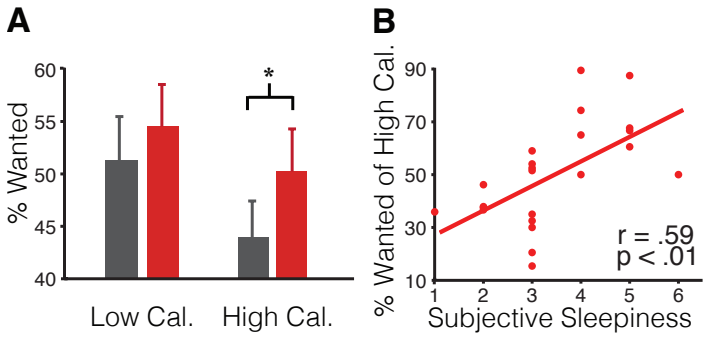

Fig 1.4) Behavioral consequences of sleep deprivation on food desirability. Behavioral responses (taken from in-scan ratings) are shown for the percentage of wanted high and low calorie items respectively (**A**) and the degree to which individual differences in sleepiness(Hoddes et al., 1973) (after sleep deprivation) predict high-calorie choices (**B**). High/low calorie items are based on median split on Calories per serving; wanted items were collapsed across "somewhat" and "strongly" wanted ratings (* indicates p<0.05; paired t-test across 23 participants; error bars show standard error).

Table 1.2) Small Volume corrections analysis

Region	T	Cluster Size	X	Y	Z	Corrected p-value
Sleep Rested > Sleep Deprived						
R Anterior cingulate	4.37	20	16	2	40	0.006
L Orbital Frontal	3.65	1	-34	48	-14	0.026
R/L Insula	4.21	6	32	22	-4	0.017
Sleep Deprived > Sleep Rested						
R Amygdala	4.39	27	18	-8	-26	0.006

Small volume correction analysis for *a priori* regions of interest taken as 8mm spheres centered at literature based ROIs (Sleep Rested < > Sleep Deprived) of the parametric contrast of want ratings (i.e. regions correlated with increasing food desire and differing by condition). The ROIs are the same as reported in the main manuscript (see Methods). Cluster size is in voxels; voxel size is 2 mm^3.

sleep rested or sleep deprived condition (r=-0.23, p=0.30, and r=-0.05, p=0.80, respectively), consistent with previous studies examining calories from snacks rather than meals (Nedeltcheva et al., 2009). Therefore, paralleling the observed change in the neural reactivity, sleep deprivation induced a concomitant behavioral profile of increased desire for weight-gain promoting (high-calorie) food choices, with inter-individual differences in the magnitude of such a change in food choice behavior being accounted for by the severity of perceived subjective sleepiness.

Discussion

Taken together, these findings establish a disrupting impact of sleep deprivation that blunts activity in established appetitive evaluation regions (Small and Prescott, 2005) within the human frontal and insula cortex during food desirability choices, yet a converse subcortical amplification of reactivity within the amygdala, known to code salience in the context of food decisions (van der Laan et al., 2011). Furthermore, these neural changes were associated with a significant increase in appetitive desire for weight-gain promoting (high-calorie) food items following sleep loss, the magnitude of which was proportional to the subjective severity of sleep loss across participants. In addition, these changes occurred despite participants consuming more calories during the sleep deprivation session (provided in a controlled manner in order to offset any increased energy expenditure). Moreover, participants' self-reported hunger levels were not different in the sleep rested and sleep deprivation session,

suggesting that the condition of sleep loss, rather than metabolic need or hunger, as a primary factor influencing the observed changes.

The characterization of these neural and behavioral changes following sleep loss may provide several explanatory insights into a central nervous system (brain) mechanism by which insufficient sleep leads to the development/maintenance of obesity.

First, these data describe a profile of bi-directional change in responsivity in appetitive-relevant brain regions following sleep deprivation. All three cortical regions of interest with recognized roles in appetitive stimulus evaluation demonstrated activity reductions following sleep loss in response to increasing food desire, while one of the two subcortical target regions of interest – the amygdala, associated with salience signaling of food items – expressed significant increases in response to food desirability. Interestingly, no significant differences in reactivity were observed in the classical reward region of the ventral striatum following sleep loss. It is important to note that while these brain areas do have specific and recognized functional roles in the context of appetitive food stimulus evaluation and choice, as we examined using the current task, theses regions are not limited to performing such functions. For example, the anterior cingulate has been associated with conflict monitoring (Botvinick, 2007) as well as autonomic (especially cardiovascular) regulation (Critchley et al., 2003), the orbital frontal cortex has been associated with inhibitory control(Stuss, 2011), the anterior insula has been associated with interoception (Craig, 2003) and the amygdala has been associated with fear and arousal processing (Zald, 2003). While our interpretation of the impact of sleep loss on these regions is made within the context of appetitive food evaluation and choice, due to the nature of the task, they may nevertheless extend beyond appetitive processes, and include alterations in other functions such as those described above.

Second, this collection of brain changes may not only help account for recognized shifts in dietary intake and altered food choices following insufficient sleep (Brondel et al., 2010), but further reconcile potentially dissonant previous findings. Specifically, prior reports have demonstrated that sleep restriction leads to increased caloric intake following sleep loss under non-laboratory or “free-living” conditions where food selection was not fixed (Brondel et al., 2010), fitting with impoverished mechanisms of appetitive evaluation and choice regulated by the frontal lobe as well as heightened salience signaling within the amygdala. However, such altered food choices following sleep loss can also occur without any significant change in ratings of the hedonic qualities of food pleasantness or food desire when smelling foods directly (Brondel et al., 2010), consistent with our observations of unaltered responding in this reward-related region of ventral striatum. Furthermore, such a neural dissociation may additionally explain why some studies have failed to observe increases in caloric intake under sleep

restriction when food choices are limited to small selection arrays and eating opportunities are fixed (Nedeltcheva et al., 2009, Schmid et al., 2009), since increases in the motivated drive to eat in the absence of food choices has been primarily associated with activity in the ventral striatum independent of the effects of sleep loss (Lawrence et al., 2012). Therefore, one plausible interpretation emerging from our data is that impoverished recruitment of cortical regions involved in appetitive choice selection following sleep loss, combined with enhanced responsivity from the amygdala, may result in improper valuation of food stimulus features, shifting behavioral choice-selection to high calorie desirable items driven more so by salience, when food is available. The current neural observations would therefore predict that if a range of freely attainable food choices and eating opportunities are offered (as is ecologically the case in the majority of real-world situations), then the effect of sleep deprivation would lead to a significant increase in food consumption choices considered non-optimal in the context of obesity (i.e. high calorie items).

Third, and congruent with these predictions, the changes in neural reactivity to food desirability under sleep deprivation were additionally accompanied by a significant shift in preferences for food items carrying the highest caloric content. While a shift in food desire ratings was observed following sleep deprivation, the controlled eating schedule of the study precluded the ability to measure actual changes in caloric intake under *ad libitum* (rather than the current controlled) food availability. Interestingly, the alteration in food desire observed here, coinciding with changes in brain activity, are consistent with previous behavioral findings describing increases in actual caloric intake following sleep loss when *ad libitum* food conditions are presented (Brondel et al., 2010, Markwald et al., 2013) and increased cravings for higher caloric food categories (e.g. sweet, salty and starchy foods) (Spiegel et al., 2004). Given the established increase in energy needs induced by sleep deprivation (Jung et al., 2011, Penev, 2012, Markwald et al., 2013), it is possible that this tendency toward increased caloric intake, and high calorie preferences reported here, supports an adaptive homeostatic function to recover such energy expended. However, a recent study which assessed *ad libitum* caloric intake as well as energy expenditure in sleep-restricted humans reported increased calorie consumption beyond that which could be explained by expended energy or altered metabolic rate (Markwald et al., 2013). Moreover, this increase in calorie intake resulted in significant gains in weight. This finding leads to the hypothesis that changes in central nervous system disruption due to sleep loss, such as the alterations in appetitive brain signaling described in the current study, may contribute to decisions that led to increased calorie consumption in excess of energy expenditure changes, one consequence of which is weight gain. We additionally demonstrated that the magnitude of change (increase) in desire for high calorie foods was positively correlated with the perceived subjective severity of sleep deprivation across

participants (indexed in the measure of sleepiness). Therefore, our data provide indirect support linking the state of sleep deprivation, and the subjective severity of this state, to altered internal homeostasis following extended time awake, and is consistent with already established alterations in metabolism and temperature regulation following sleep loss (Knutson et al., 2007, Romeijn et al., 2012). This may reflect a progressive deterioration in the brain and body systems that regulate and maintain optimal energy balance, potentially reflected in the current study by increases in energy consumption through heightened desire for high calorie foods.

Finally, and related to such whole organism considerations, elegant prior work has describe peripheral body changes in appetite and metabolic regulating hormones following sleep loss that can lead to weight-gain (Knutson et al., 2007, Van Cauter et al., 2007, Hanlon and Van Cauter, 2011). Our findings raise the presence of a central nervous system dysfunction that stands along side these increasingly well-described peripheral body changes following sleep deprivation that together, may converge on a common impact sleep loss on weight-gain potential.

Beyond the implications stated above, it is important to note that the current findings should be considered in the context of several limitations. First, this study used a carefully controlled feeding schedule that was standardized across participants which did not allow us to assess actual changes in calories consumed due to sleep deprivation (although see (Brondel et al., 2010, Markwald et al., 2013)) or to assess he relationship between the neural responses observed and behavioral shifts in actual calories consumed. Furthermore, due to this limitation it will be important for future studies to assess whether access to *ad libitum* high calorie food would normalize the observed brain responses under sleep deprivation due to potentially reduced motivational demands for high-calorie items after consumption. Second, all scan sessions for this study took place during the morning. Since both appetite and sleep patterns are significantly influenced by circadian phase (Saper, 2006), future studies will be needed to examine the interactions of measurements at different circadian phases. Indeed, recent behavioral studies indicate that the largest impact of sleep loss on altered food choices occurs during the evening (Baron et al., 2011, Markwald et al., 2013) leading to the testable hypothesis that changes observed in the current study would be further exaggerated when repeated later in the day. Finally, it should be noted that the current findings were measured in a group of healthy young and lean participants (20.5±1.8 s.d. years of age; 23.0±1.8 s.d. BMI). An important future challenge will be to examine whether similar alterations caused by sleep deprivation are expressed across a broader age and body mass range; pertinent considering that hormones, metabolism as well as neural responses change over the life span (Wilson and Morley, 2003), and across a spectrum of lean to obese ranges (Wang et al., 2009).

In summary, these findings contribute to a novel brain mechanism by which sleep loss may lead to the development and/or maintenance of obesity through the potentially maladaptive selection of foods carrying obesogenic (weight-gain) potential, thereby explaining the large-scale significant association between reduced sleep time and obesity reported in population level studies (Cappuccio et al., 2008). They further support the proposal of sufficient sleep as an important mechanistic factor promoting weight control, one pathway of which appears to be the regulation of central brain mechanisms governing appropriate food choices.

Chapter 2

The neural and behavioral impact of sleep deprivation on processing of monetary rewards and punishments

Introduction

Reward represents a guiding principal governing a broad array of human behaviors. Optimal interpretation of reward signals to be approached, and punishments to be avoided, supports decisions and actions that favor survival (Berridge and Robinson, 2003, Schultz, 2006, Knutson and Wimmer, 2007a). However, reward-seeking can lead to deleterious and life-threatening behaviors, exemplified by abusive drug addiction, impulsive thrill seeking and adverse risk taking (Schultz, 2006, Volkow et al., 2007). Furthermore, emerging evidence now also shows sleep to be an important regulator of this reward system, with sleep loss as a potential risk factor in the development of reward system disorders (Perogamvros and Schwartz, 2012).

A rich research literature has now characterized the neural mechanisms mediating incentivized behavior and reward processing. From this work has emerged common pathways within the mesolimbic system across all mammalian species that, when electrically stimulated, unconditionally elicits either approach or avoidance behavior (Panksepp, 1998). Approach behaviors can be instigated by stimulating projections of the midbrain dopamine neurons ascending from the ventral tegmental area (VTA) to the ventral striatum, including the nucleus accumbens (NAcc) (Panksepp, 1998, Ikemoto and Panksepp, 1999). In contrast, avoidance behaviors, can be elicited by stimulation of a separate pathway, descending from the anterior insula and basolateral amygdala through the stria terminalis to the periaquiductal grey (Panksepp, 1998).

Given that separate neural mechanisms support approach and avoidance behavior, functional MRI (fMRI) techniques have been designed to isolate the study of these separate pathways in the human brain (Knutson et al., 2001a, Yacubian et al., 2006). In particular, monetary incentives have proven reliable tools for the study of incentive processes (Knutson and Cooper, 2005, Knutson and Greer, 2008). A meta-analysis of 21 human neuroimaging studies using the monetary incentive delay task or a similar paradigm, revealed dissociable pathways responding to monetary gain and loss that strongly converge with incentive circuits identified in other mammalian species using electrical stimulation. These regions included the NAcc during the anticipation of gain, and conversely, sub-regions of the anterior insula for the anticipation of loss. Demonstrating that event-related fMRI incentive paradigms, in particular the monetary incentive delay (MID) task, provides a potent methodology for probing functional changes in mesolimbic reward networks of the human brain and specifically for disambiguating processes related to gain and loss.

While there are several studies that now characterize an impact of sleep deprivation on monetary risk taking, to date, these studies have primarily used

mixed stimuli where the relative contributions of gain seeking or loss aversion cannot be teased apart. Furthermore, there has also not been a clear investigation of the reactivity to the anticipatory trial phase and the outcome trial phase on a trial-by-trial basis. This is an important distinction because the anticipatory incentive signal may contain more information about individual choice tendencies (e.g. being drawn to rewards or away form losses) and the outcome incentive signal may hold more information about integration of incentive information and potentially incentive learning. In order to distinguish between these aspects of incentive processing, the current study employed the monetary incentive delay (MID) task under conditions of sleep deprivation as well as rested sleep in order to test the hypothesis that sleep deprivation will lead to dissociable alterations in the mesolimbic responses to 1) gain anticipation in the NAcc, 2) loss anticipation in the anterior insula, 3) gain outcome in the medial prefrontal cortex (MPFC) and 4) loss outcome in the anterior insula.

Methods

Methods overview: Thirty-five participants either completed a night of normal rested sleep recorded with polysomnography in the laboratory (N=18; 8 female; age 20.1+-2.0sd) or a night of total sleep deprivation monitored in the lab by laboratory personnel as well as objective wrist actigraphy (N=17; 11 female; age 20.6+-1.5sd). In the morning of either session each participant completed an fMRI session (average scan time 9:30 AM) where they completed the monetary incentive delay task (**Fig IV.i** in *Common Methods*). In order to assess brain responsivity to monetary gain and loss anticipation, fMRI BOLD signal was correlated with monetary value for gain and loss separately on a trial-to-trial basis at the time of the cue presentation. In addition neural responses to outcomes, or receipt, of monetary reward was assessed by modeling responses to gain versus non-gain outcomes and loss v s. non-loss outcomes separately. All monetary delay task procedures as well as fMRI acquisition, preprocessing and modeling procedures can be found in section *IV. Common Methods.*

ROI Definition & Analysis: In accordance with recommended ROI reporting policies (Poldrack, 2007), regions of interests were taken as the average parameter estimates from 4 mm spheres centered around MNI coordinates from previous literature on reward-motivated action (Harsay et al., 2011) for the ventral striatum (L: -12, 18, -8; R: 6, 10, -6) as well as monetary outcome processing in the medial prefrontal cortex (R: 6, 46, 4)(Knutson et al., 2001b). An area of the right anterior insula sensitive to loss evaluation (Wu et al., 2011) was used to asses responses to both loss anticipation and loss outcome processing in this study (R: 36, 27, -1). All of these regions have substantial dopaminergic innervation, and have been reliably linked to motivated behavior (Haber and Knutson, 2010).

Results

Neural response to anticipation under sleep deprivation: While both sleep rested and sleep deprived groups equally robustly activated the NAcc in response to monetary gains, there were no observable differences in responding between the two sleep groups. This was true both in the region of interest analysis (**Fig 2.1A**) and when looking at whole brain differences at a low threshold (**Table 2.1**; p<0.001 uncorrected). Similarly, in the anterior insula, there were no systematic differences in loss anticipation activation between the sleep groups either at ROI level (**Fig 2.1B**) or the whole brain level (**Table 2.1**; p<0.001 uncorrected). Finally, to verify that there were no differences in neural activations to incentive anticipation due to sleep deprivation in any brain regions, we performed a whole brain analysis (p<0.05 FWE corrected). Taken together these data indicate that there are no systematic differences in incentive anticipation due to sleep deprivation when gains and losses are isolated in separate trials and when no choice is required.

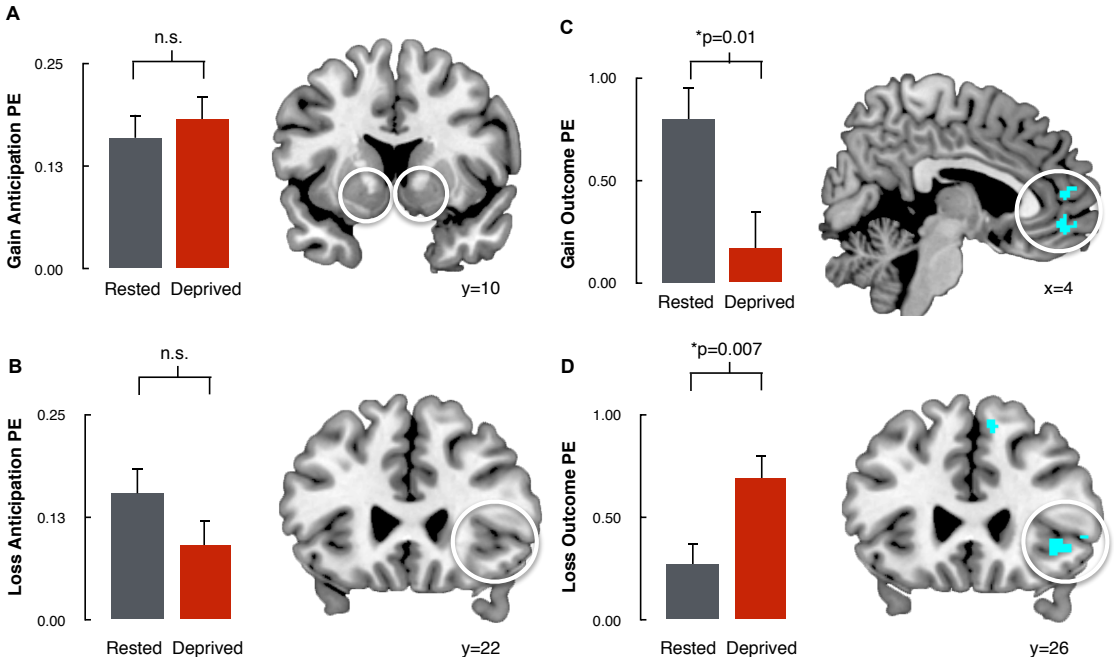

Fig 2.1) Neural consequences of sleep deprivation on processing of monetary gains and loss. Sleep deprivation led to no significant group differences in either gain anticipation in the nucleus accumbens (**A**) or loss anticipation in the right anterior insula (**B**). Sleep deprivation led to a significant decrease in responding of the medial prefrontal cortex to monetary gain outcomes (**C**) and a significant increase in the response of the right anterior insula in response to monetary loss outcomes (**D**). Whole brain analysis is thresholded at p<0.005 for display purposes for group comparisons of sleep deprivation compared to sleep rested. Region of interest analysis (bar graphs) are mean parameter estimates with standard errors of the mean extracted from 6mm spheres centered at foci taken form previous literature (See ROI methods; circles indicate general areas of interest not specific foci; error bars show standard error).

Neural response to gain outcomes under sleep deprivation: Sleep deprivation led to a marked decrease in responsivity of the MPFC to the receipt of monetary gains (i.e. winning $0.20, $1 or $5) compared to non-gain outcomes (i.e. missing the opportunity to win and receiving $0) (**Fig 2.1C**). In contrast to this diminished activity seen in the MPFC, the anterior insula showed an amplification of activity under sleep deprivation in response to the outcome of losing money as compared to a non-loss outcome (**Fig 2.1D**). Taken together, there was a significant disruption in the neural processing of the receipt of monetary incentives such that there was a simultaneous diminished responsivity to the receipt of monetary gains and an amplified responsivity to the receipt of monetary losses.

Discussion

In summary, while anticipatory reactivity remained unchanged after sleep deprivation, neural responses to the receipt of monetary gains and losses showed a significant change. Specifically, the medial prefrontal cortex showed a decrease in sensitivity to positive events while the anterior insula showed an increase in sensitivity to negative events following sleep deprivation.

To date, investigations into the neural consequences of sleep deprivation on incentive processing have largely focused on paradigms that combine potential gain and loss outcomes in order to assess risk taking behavior (Killgore et al., 2006, Venkatraman et al., 2007a, Venkatraman et al., 2011, Mullin et al., 2013). These studies attributed observed neural and behavioral shifts in risk taking to changes in valuation of gains (specifically, increases) and losses (specifically, decreases). However, more recent reports have questioned the gain/loss valuation hypothesis due to new contradictory evidence (Menz et al., 2012, Libedinsky et al., 2013). After distinguishing anticipation of gains and losses in distinct trials, we did not observe group-level effects of sleep deprivation on neural activity during anticipation of either monetary gains or monetary losses. Therefore, a more parsimonious explanation for previous findings may be that sleep deprivation reduces peoples' ability to integrate competing incentives (i.e. gains and losses), rather than a biased perception of either gain or loss individually. Such an account is additionally consistent with evidence that responses to conflict (i.e. cognition associated with processing conflicting options) are decreased under sleep deprivation (Menz et al., 2012). Importantly, although effects may not be evident at the group level, trait differences may still bias incentive processing on the individual level.

One possible explanation for the lack of group differences in incentive anticipation under sleep deprivation is that there may be large individual differences in sleep deprivation response that serve to mask the effects of the group difference. It is well know that sleep deprivation can lead to increased

variability in subject responses, however, it is unclear what drives the variability (Durmer and Dinges, 2005). Genetic variation, particularly in the dopamine systems, presents an intriguing possibility given the known associations with this system in both reward processing (Dreher et al., 2009, Aarts et al., 2010, Stice et al., 2012) and sleep regulation (Holst et al., 2014). **Chapter 3** will test this emerging hypothesis in a subset of the participants reported on here who have been genotyped to identify natural variation in the dopamine transporter gene.

Looking next at the responses to monetary outcomes under sleep deprivation, reveals both a decreased sensitivity to monetary gain outcomes in the MPFC as well as an increased sensitivity to monetary losses in the anterior insula. The medial prefrontal cortex has been previously demonstrated to be important for learning from feedback and goal maintenance (Hitchcott et al., 2007), thus a lack of responsivity to monetary feedback in this brain area may be indicative of a reduce capacity to learn from incentives as a result of sleep deprivation which may underlie previous reports of poor incentive decision making under sleep deprivation. In contrast the anterior insula displayed an increased response to monetary loss, perhaps in line with previous accounts of an amplified negativity bias under sleep deprivation (Yoo et al., 2007, Goldstein et al., 2013). Taken together these data led to the hypothesis that under sleep deprivation, there may be a deficit in the ability to learn from monetary gains while there may be an amplified sensitivity and ability to learn form monetary losses. This hypothesis is specifically tested in **Chapter 4** of this report.

Considering this evidence in the broader context of this report we see that the lack of a significant difference in NAcc responding to monetary gain anticipation seen here is in line with the similar lack of sleep dependent responding in the NAcc to desirable food stimuli presented in **Chapter 1**. Furthermore, the decreased responding to monetary gain outcomes under sleep deprivation reported here is in line with the decreased responding of frontal regions to desirable foods in **Chapter 1**, although it should be noted that these were non-overlapping regions within the frontal cortex. Finally, the reactivity of the anterior insula under conditions of sleep deprivation presents the more complicated story. Specifically, under sleep deprivation the anterior insula showed diminished activity to desirable food stimuli, no change in activity to the anticipation of monetary loss, and finally a significant increase in activity to the receipt of monetary losses. This differential responding (even within overlapping participants) highlights the importance of understanding context specific interactions when assessing the influence of sleep deprivation on incentive processing. Furthermore, this highlights the potential importance of sleep in facilitating integration of information, which may underlie these diverse results.

The pattern of results across both this chapter and **Chapter 1** presents an intriguing possibility that one general effect of sleep deprivation may be to shift

the balanced of networking incentive brain processing toward heightened subcortical activity, and diminished cortical activity, which is in agreement with several other reports in different topic domains (Drummond et al., 2005, Yoo et al., 2007, Gujar et al., 2011b). While these studies alone are unable to define the precise underlying neurobiological mechanism for this change in activity profile, at least two theoretical underlying mechanisms are worthy of consideration. 1) The neuro-cellular systems level which differs between cortical and subcortical areas may be differentially affected by sleep deprivation. 2) The regional connectivity level which may determine how and when regional brain areas are recruited under sleep deprivation. In support of the second idea, previous reports have described diminished connectivity between cortical and subcortical areas resulting in increased subcortical activation (Yoo et al., 2007, Gujar et al., 2011b). Interestingly, the pattern in the anterior insula of both increased, sustained as well as decreased activation under sleep deprivation depending on the incentive context may offer further support of regional brain connectivity disruption under sleep deprivation. Thus, the anterior insula may be more or less recruited by other brain areas depending on the context.

As discussed above, these results open important unanswered questions as to 1) the nature of individual genetic differences in gain and loss anticipatory reactivity and 2) the consequences of diminished gain outcome and increased loss outcome sensitivity on incentive reinforcement learning. These topics will be specifically tested and discussed in the next two chapters.

Table 2.1) Sleep Rested > Sleep Deprived. Exploratory whole brain analysis

Region	T	Cluster Size	X	Y	Z
Gain Anticipation					
R Lingual Gyrus	4.57	144	16	-62	10
	3.74		22	-68	18
L Cerebellum	4.33	40	-40	-40	-44
L Inferior Frontal lobe	4.27	32	-46	12	18
L Inferior Frontal lobe	4.20	30	-32	10	22
	3.59		-24	20	22
L Cerebellum Vermis	3.98	44	-2	-70	-16
Loss Anticipation					
R Fusiform Gyrus	4.26	57	24	-78	-10
	3.64		12	-82	-6
L Inferior Frontal Opercular	4.23	38	-26	2	26
R Lingual Gyrus	3.80	26	4	-60	12
L Middle Frontal	3.77	22	-24	16	30
Gain Outcomes					
L Superior Frontal	5.09	54	-18	44	38
R Inferior Frontal Opercular	4.79	28	54	14	2
R Fusiform	4.56	94	40	-44	-22
R Middle Frontal	4.36	47	24	48	32
R Medial Frontal	4.33	154	12	52	10
	4.28		2	50	10
	4.20		6	50	-2
L Supramarginal	3.62	29	-60	-36	26
	3.56		-64	-28	20
Loss Outcomes					
L Postcentral Gyrus	4.14	30	-66	-18	24

Exploratory whole brain analysis showing all peak activations (MNI coordinates) significant at $p<0.001$ uncorrected ($20mm^3$ cluster criteria) for paired comparison (Sleep Rested > Sleep Deprived) of the parametric contrast of gain anticipation, loss anticipation, gain outcomes (non-gain < gain) and loss outcomes (non-loss > loss).

Table 2.2) Sleep Deprived > Sleep Rested. Exploratory whole brain analysis

Region	T	Cluster Size	X	Y	Z
Gain Anticipation					
R Frontal Middle Gyrus	4.32	69	48	16	52
	3.94		46	24	50
	3.64		42	12	58
L Frontal Middle Gyrus	4.16	26	-48	26	46
Loss Anticipation					
None					
Gain Outcome					
None					
Loss Outcome					
Cerebelum	5.25	88	24	-72	-28
R Fusiform	4.81	141	28	-64	-12
	4.23		36	-52	-12
	3.98		30	-74	-2
L Cerebellum	4.69	76	-12	-82	-28
	3.58		-8	-88	-32
L Cerebellum	4.64	49	-32	-66	-28
	3.49		-38	-68	-34
R Inferior Orbital Frontal	4.59	42	38	24	-8
L Middle Frontal	4.57	114	-44	56	18
	4.01		-22	66	24
	3.78		-34	60	22
R Superior Medial Frontal	4.56	24	10	26	52
R Anterior Cingulate	4.48	186	2	48	12
	4.14		-8	36	24
	4.10		-2	60	20
L Anterior Cingulate	4.48	78	-6	36	-6
	4.38		6	36	-6
R Superior Frontal	4.40	43	18	66	30
R superior Frontal	4.34	30	16	40	50

L Middle Occipital	4.33	74	-24	-96	14
	3.83		-16	-106	8
	3.55		-18	-98	8
R Cerebellum	4.31	23	12	-80	-24
L Cerebellum	4.21	20	-6	-60	-38
L Medial Superior Frontal	4.19	84	-2	38	44
	4.18		-10	38	52
L Middle Temporal	4.12	59	-62	-56	4
R Angular gyrus	4.12	22	50	-50	34
R Middle Frontal	4.08	31	30	6	44
L Middle Cingulate	3.96	27	-6	-24	26
L Posterior Cingulate	3.96	21	-6	-34	20
R Middle Cingulate	3.94	67	6	-6	32
R Superior Frontal	3.88	20	26	66	18

Exploratory whole brain analysis showing all peak activations (MNI coordinates) significant at $p<0.001$ uncorrected ($20mm^3$ cluster criteria) for paired comparison (Sleep Rested < Sleep Deprived) of the parametric contrast of gain anticipation, loss anticipation, gain outcomes (non-gain < gain) and loss outcomes (non-loss > loss).

Chapter 3

The interaction of sleep deprivation and a genetic polymorphism of the human dopamine transporter on neural anticipation of monetary rewards and punishments

Introduction

Dopamine-related brain circuits modulate approach towards rewards and avoidance of punishments, thus guiding motivated behaviors (Nitschke et al., 2006, Knutson and Greer, 2008). Dopaminergic projection areas in the nucleus accumbens (NAcc) and anterior insula have consistently been implicated in the anticipation of gains and losses. Further, abnormal responses in these neural circuits—due to genetics, disease, or environmental factors—have been linked to a range of disadvantageous outcomes, including suboptimal risk-taking, deficits of attention, mood disturbance, and addiction (Knutson and Greer, 2008).

Independent of these findings, emerging evidence indicates that sleep deprivation can disrupt dopaminergic function by modifying dopamine receptor sensitivity and availability (Tufik, 1981, Volkow et al., 2012). However, neural evidence that sleep deprivation alters brain activity during incentive processing, particularly in the NAcc and anterior insula, has been inconsistent—with some reports demonstrating significant disruptions (Venkatraman et al., 2007b, Venkatraman et al., 2011, Mullin et al., 2013), but others indicating a lack of significant changes (Libedinsky et al., 2011, Menz et al., 2012, Libedinsky et al., 2013). However, as reported in Chapter 2, when gain and loss anticipation are properly isolated we do not see systematic differences in reward system responding under sleep deprivation.

One possible explanation for this is that individual differences (including genetic polymorphisms that alter incentive brain processing) may interact with sleep deprivation, obscuring differences when not explicitly considered. One candidate for individual differences in dopamine function involves the polymorphism on the dopamine transporter (DAT) gene, which has been associated with altered dopamine availability (Aarts et al., 2010). Individual differences in this genetic polymorphism may therefore modulate incentive brain processing during sleep deprivation, due to the functional influence of the DAT polymorphism on (a) synaptic dopamine function, (b) brain reactivity to reward (Aarts et al., 2010), and (c) sleep homeostasis (Holst et al., 2014). Further, characterizing the interaction between trait dopamine genetics, sleep deprivation and reward brain activity has potential clinical importance, since sleep disruption is highly co-morbid with numerous psychiatric and neurological conditions associated with dysregulated dopaminergic reward processing, including Parkinson's disease, attention hyperactive deficit disorder (ADHD), and substance abuse (Perogamvros and Schwartz, 2012, Moreau et al., 2013).

One method used to assess individual differences in dopaminergic function involves examining functional genetic polymorphisms, which constitute naturally occurring variations in alleles that can lead to altered gene expression and thus

function (Dreher et al., 2009). While several genes affect dopamine action, the dopamine transporter (DAT) gene polymorphism is particularly well-suited for examining the interaction between striatal dopamine function and sleep loss. DAT is a protein that clears synaptic dopamine after release in the striatum, homeostatically governing the fidelity of dopamine signaling (Williams and Galli, 2006). Evidence from human radioligand studies (Heinz et al., 2000); but see also (Jacobsen et al., 2000)) and *in vitro* models (VanNess et al., 2005) demonstrate that carrying at least one allele characterized by nine tandem repeats of a nucleotide base pair sequence on the 3' untranslated region of the DAT gene ("9R carriers") results lower levels of DAT protein and therefore higher dopamine synaptic availability, while having homozygous alleles with ten tandem repeats ("10R homozygotes") results in lower dopamine synaptic availability. Moreover, the highest concentrations of DAT are found within the striatum (Ciliax et al., 1999, Williams and Galli, 2006), and human neuroimaging studies have demonstrated alterations in both striatal activity and mesolimbic and related cortical functional connectivity that depends on the DAT polymorphism (Dreher et al., 2009, Aarts et al., 2010, Zhong et al., 2012). Offering a further link with sleep and sleep deprivation, DAT function is necessary for the wake-promoting properties of stimulants such as cocaine and modafinil, including under sleep deprivation (Wisor et al., 2001), and recent evidence demonstrates that the DAT polymorphism has functional effects on sleep homeostasis (Holst et al., 2014). Thus, investigating individuals with trait differences in the DAT polymorphism offers a unique human *in vivo* opportunity (advocated when studying candidate gene targets (Meyer-Lindenberg, 2012)) to examine dopamine-related incentive brain functioning following sleep deprivation.

Combining an established incentive paradigm independently assessing gain and loss with functional MRI (fMRI), here we investigated the differential affects of sleep deprivation on gain anticipation processing within the nucleus accumbens, and loss anticipation processing within the anterior insula. We tested the hypothesis that individual trait differences in the dopamine transporter gene—associated with altered dopamine availability—confer a significant sleep deprivation vulnerability-interaction in such gain and loss incentive processing.

Methods

Methods overview: Twenty-nine participants who had been genotyped were included in this analysis (17 female; mean age: 20.5± 1.8 s.d; 3 participants were left handed).Each participant either completed a night of normal rested sleep recorded with polysomnography in the laboratory (N=15) or a night of total sleep deprivation monitored in the lab by laboratory personnel as well as objective wrist actigraphy (N=14). In the morning of either session each participant completed an fMRI session (average scan time 9:30 AM) where they completed the monetary incentive delay task (**Fig IV.i** in *Common Methods*). In order to assess

brain responsivity to monetary gain and loss anticipation, fMRI BOLD signal was correlated with monetary value for gain and loss separately on a trial-to-trial basis at the time of the cue presentation. In addition neural responses to outcomes, or receipt, of monetary reward was assessed by modeling responses to gain versus non-gain outcomes and loss v s. non-loss outcomes separately. All sleep monitoring procedures as well as monetary delay task procedures, fMRI acquisition, preprocessing and modeling procedures can be found in section *IV. Common Methods.*

Genetic analysis: In order to assess this genetic variation, saliva samples were collected from participants using Oragene kits (DNA Genotek Inc, Ottawa, Onterio, Canada) after the experimental session. DNA extraction was then carried out by the Functional Genomics laboratory at the University of California, Berkeley and genotyping was performed by the Institute for Human Genetics at the University of California, San Francisco. The polymorphism on *SLC6A3/DAT1* includes a 40-bp variable number of tandem repeats (VNTR) in the 3' untranslated region of the gene that is repeated between 3 and 13 times, with the greatest frequency being either 9 repeats (9R) or 10 repeats (10R) (Dreher et al., 2009). This information was used to classify participants into two groups 1) those who were homozygous for the 10R allele, and 2) those who were either homozygous for the 9R allele or who had one copy of the 9R allele and one copy of the 10R allele (i.e. 9R carriers). No participants carried any other number of VNTR alleles. Participant counts in each genotype and sleep group are included above in the participant section. The percentage of 10R homozygotes and 9R carriers in our sample was consistent with percentages in previous reports (Dreher et al., 2009, Stice et al., 2012, Holst et al., 2014).

After genotyping, participants were separated into four groups according to sleep condition (rested or deprived) and genotype status (9R or 10R/10R; see genetic analysis below for details): 1) Sleep rested & 10R/10R: N=7, age 20.86+-2.9sd, 2 female, 2) Sleep deprived & 10R/10R: N=7, age 20.86+-1.8sd, 6 female, 3) Sleep rested & 9R: N=8, age 19.63+-1.2sd, 5 female, and 4) Sleep deprived & 9R: N=7, age 20.57+-1.3sd, 4 female.

ROI Definition & Analysis: In accordance with recommended ROI reporting policies (Poldrack, 2007), regions of interests were taken as the average parameter estimates from 4 mm spheres centered around MNI coordinates from previous literature on reward-motivated action (Harsay et al., 2011) for the ventral striatum (L: -12, 18, -8; R: 6, 10, -6), and loss anticipation (Wu et al., 2011) for the right anterior Insula (R: 36, 27, -1). Both of these regions have substantial dopaminergic innervation, and have been reliably linked to motivated behavior (Haber and Knutson, 2010). The parameter estimates from the voxels in these regions of interest were averaged for each subject and then entered into a two-way analysis of variance across subjects using the MATLAB (Mathworks Inc.)

function anova2 with factors of sleep condition (rested or deprived) and DAT status (10R homozygous or 9R carriers).

Results

Effects of sleep deprivation and dopamine polymorphism on gain anticipation: Consistent with several previous reports (Libedinsky et al., 2011, Menz et al., 2012, Libedinsky et al., 2013) and as reported in **Chapter 2**, sleep deprivation did not have a significant main effect on NAcc ROI activity during the anticipation of monetary gain, relative to the rested condition (**Fig 3.1A**). However, supporting the experimental hypothesis, there was a significant Sleep-condition by Genotype interaction for NAcc activity during anticipation of monetary gain (p=0.01; **Fig 3.1B**). Post-hoc t-tests revealed that the 9R carriers—associated with elevated phasic striatal dopamine—expressed significantly amplified reward responsivity relative to the 10R homozygotes following sleep deprivation (p=0.005), as well as the 9R carriers in the sleep rested condition (p=0.05). No significant changes in NAcc reward-reactivity were observed across sleep conditions in the 10R homozygotes (p=0.13).

Therefore, markedly different NAcc reward responses were observed following sleep deprivation depending on the DAT functional polymorphisms, with elevated trait-synaptic dopamine (represented by the 9R carriers) leading to heightened striatal reward-reactivity under conditions of sleep deprivation, relative to the 10R homozygotes.

Effects of sleep deprivation and dopamine polymorphism on loss anticipation: As with monetary gain, no significant main effects of sleep deprivation were identified during monetary loss anticipation in anterior insula activity, and as

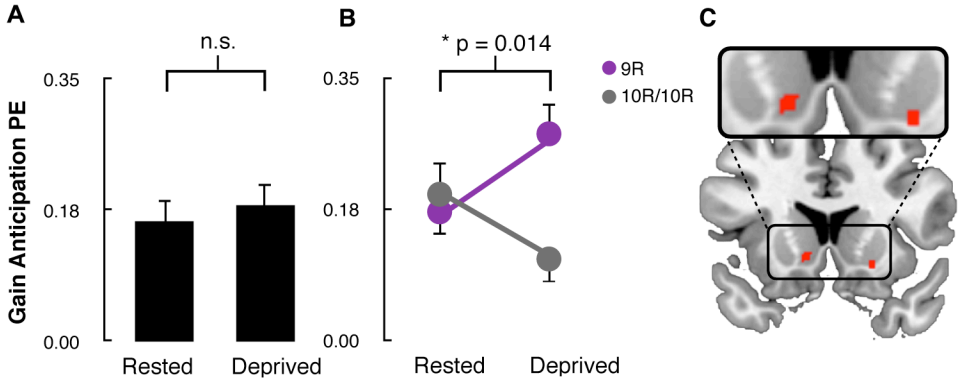

Fig 3.1) Neural responses to gain anticipation in the nucleus accumbens by sleep condition and genotype. Overall, nucleus accumbens activity showed no sleep condition differences during gain anticipation (**A**), however, there was a significant sleep condition (rested or deprived) by DAT genotype (9R or 10R/10R) interaction of activity during gain anticipation (p=0.01) (**B & C**).

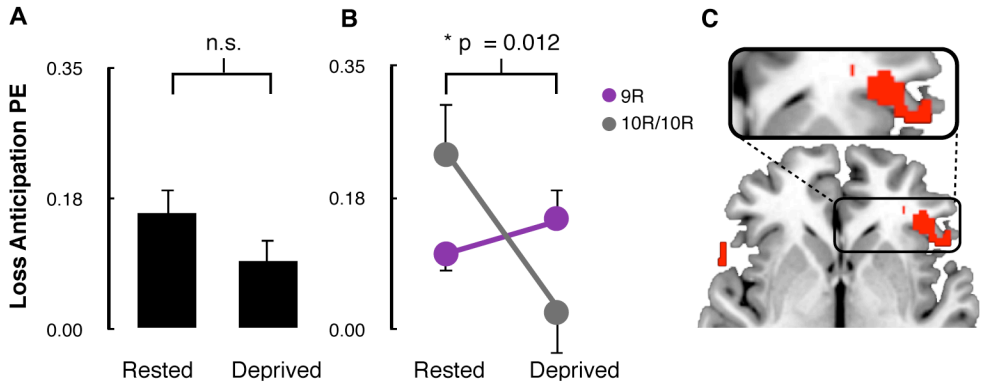

Fig 3.2) Neural responses to loss anticipation in the anterior insula by sleep condition and genotype. Overall, anterior insula activity showed no sleep condition differences during loss anticipation (**A**), however, there was a significant sleep condition (rested or deprived) by DAT genotype (9R or 10R/10R) interaction of activity during loss anticipation (p=0.01) (**B & C**).

reported in **Chapter 2** (**Fig 3.2A**). However, consistent with the experimental hypothesis, there was a significant Sleep-condition by Genotype interaction in anterior insula activity during loss anticipation (p=0.01; **Fig. 3.2B**). While similar to the interaction for gain reactivity in the NAcc, post-hoc t-tests revealed that the loss-dependent anterior insula interaction was driven by the 10R homozygous group—those associated with reduced synaptic striatal dopamine—expressing a significant reduction in loss anticipation reactivity under sleep deprivation compared to the sleep rested condition (p=0.03). There were no significant differences in loss activity in the anterior insula between the rested and deprived conditions in the 9R carrier group, and non-significant trends in response difference between the two genetic groups in the sleep rested condition (p=0.075), and between the two genetic groups in the sleep-deprived condition (p=0.085).

Thus, similar to activity in the NAcc, significantly different anterior insula response profiles were observed following sleep deprivation depending on the DAT functional polymorphisms. Specifically, reduced trait-synaptic dopamine (represented by the 10R homozygotes) resulted in a blunted anterior insula activity following sleep deprivation, relative to the sleep rested condition.

Discussion

This study provides an initial exploration of interactions between sleep deprivation and genetics on incentive processing. Despite a relatively modest sample size, these findings provide preliminary evidence of the interactive influence of genetic trait dopaminergic variants and sleep deprivation on neural processing of rewards and punishments.

While sleep deprivation did not significantly alter incentive brain processing at the group level (see **Chapter 2**), when dopamine genotype subgroup was

considered, significant interactions emerged. For NAcc activity during gain anticipation, sleep-deprived individuals with 9R DAT polymorphism (associated with more phasic dopamine) showed enhanced responses relative to either 9R carriers under sleep rested conditions or to 10R/10R homozygotes (associated with less phasic dopamine). Therefore, the impact of sleep loss on striatal reward processing was not universal, but instead depended on the trait dopamine-regulating genotype status of individuals.

This finding offers several mechanistic insights into reward brain processing under conditions of sleep loss. First, sleep deprivation has previously been shown to reduce the availability of dopamine D2/D3 receptors in the human striatum(Volkow et al., 2012), which could suggest a potential mechanism underlying the current findings. Specifically, the unique combination of elevated phasic dopamine (here, the 9R carriers), and reduced availability of D2/D3 receptors after sleep deprivation (Volkow et al., 2012), may consequently increase the availability or receptivity of remaining D1 receptors, resulting in enhanced reward-reactivity in the striatum. This appears further tenable considering that activation of postsynaptic D1 receptors may preferentially increase striatal fMRI signal (Knutson and Gibbs, 2007). Second, since D2 receptors can facilitate DAT functioning (Williams and Galli, 2006), sleep loss-related reductions of D2 receptors may impair the efficacy of the dopamine transporter protein on an individual genotype-specific basis. As a result, sleep deprivation may exaggerate deficits of the dopamine transporter protein in the 9R group, resulting in increased phasic dopamine availability, resulting in an increase in NAcc reward reactivity following sleep deprivation. Third, sleep deprivation may decrease tonic dopamine (Miller et al., 1983), “unmasking” individual differences in phasic dopamine. While each of these mechanisms is distinct, they could also interact to produce the observed findings. Some combination of these accounts might provide a mechanistic explanation of how changes in dopamine function due to sleep deprivation can ultimately lead to individual level interactions with DAT genotype.

Genotype interactions with sleep deprivation were not limited to reward processing, but also occurred in the context of punishment. Specifically, while sleep deprivation did not influence anterior insula activity during anticipation of loss at the group level, a significant interaction again emerged after accounting for individual differences in the DAT polymorphism. In contrast to the interaction of NAcc activity during gain anticipation and sleep deprivation in the 9R carriers, this interaction was driven by diminished anterior insula activity during loss anticipation in sleep-deprived 10R carriers, relative to rested conditions. In contrast, 9R carriers displayed no significant changes in anterior insula activity during loss anticipation, suggesting resilience to the impact of sleep deprivation.

Several lines of evidence may offer mechanistic insights explaining the genotypic difference between the 9R carriers and 10R homozygotes during loss anticipation. The insula, particularly the anterior (agranular) region, receives dense dopamine innervation from brainstem nuclei. Further, dopaminergic projections to this area appear necessary for certain forms of avoidance (rather than approach) behavior (Zito et al., 1988, Treadway et al., 2012). Therefore, the increased phasic dopaminergic activity within the 9R carriers may confer a protective benefit to the effects of sleep deprivation during loss anticipation, in contrast to enhanced phasic dopaminergic activity in the striatum during gain anticipation. As a consequence, elevated phasic dopamine action in the anterior insula of 9R carriers may negate the normal blunting of loss sensitivity caused by sleep loss seen in 10R homozygotes.

Together, individuals show opposing alterations in neural responses during anticipation of gains and losses on the basis of genotype. Specifically, DAT 9R carriers show increased neural responses during gain anticipation (with no changes during loss anticipation), while 10R homozygotes show decreased neural responses during loss anticipation (with little change during gain anticipation). Interestingly, both of these profiles could promote reward seeking in the face of mixed incentives (i.e. gain and loss trade-offs, combined), consistent with behavioral findings (Killgore et al., 2006, McKenna et al., 2007). However, the current findings suggest that these two genetic sub-groups may express a similar behavioral phenotype through different underlying mechanisms.

More generally, these findings may be of clinical relevance when considering disorders in which the DAT genetic polymorphism presents a known risk factor with concomitant sleep disruption. Known risks include disorders like ADHD (Sharp et al., 2009) and symptoms related to substance abuse (i.e., cue-induced craving and withdrawal; (van der Zwaluw et al., 2009)). In these cases, sleep disruption presents a potentially compounding risk factor, which may generate divergent pathological profiles, and thus different therapeutic responses to sleep restorative interventions, depending on an individual's dopaminergic genotype.

For example, NAcc activity during reward anticipation is blunted in individuals with ADHD (e.g., (Scheres et al., 2007)), and representation of 9R carriers is increased (Franke et al., 2009). NAcc activity during reward anticipation, however, is apparently not significantly influenced by DAT genotype in children with ADHD (Hoogman et al., 2013). Given recognized sleep disruptions in ADHD (Moreau et al., 2013), the present results imply that sleep deprivation might "unmask" genetic influences on the striatal function of individuals afflicted with ADHD. If correct, such findings might indicate that sleep disruption and dopaminergic genotype are interactive risk factors as well as therapeutic targets for relevant disorders.

Chapter 4

The impact of sleep deprivation on reinforcement learning from monetary reward and punishment feedback

Introduction

Learning what in the environment should be approached, and what should be avoided, represents a fundamental survival principal across most all species, including humans (Haber and Knutson, 2010, Maia and Frank, 2011). One way that the brain acquires such knowledge is through trial and error. This process is supported by fronto-striatal-midbrain networks, the underlying dynamics of which have further been described by computational models of reinforcement learning. Despite evidence indicating that sleep deprivation impairs forms of hippocampal learning (Walker and Stickgold, 2006), no study to date has investigated the role of sleep in preparing the brain for next day reinforcement learning. Translationally, this may be of special relevance in the context of understanding the interaction between co-morbid sleep disruption and addiction disorders, where learning about the reinforcing properties of a drug stimulus represents a significant contributing mechanism (Park et al., 2010, Maia and Frank, 2011).

Reinforcement learning refers to a specific algorithm (originally identified by computer scientists) by which information about a stimulus is adaptively learned by trial-and-error based exposure to rewarding or punishing feedback from that stimulus (Sutton, 1998). This algorithm relies on repeated exposure to a stimulus such that, on each exposure, a prediction is made as to the value of the stimulus and the outcome of the interaction is compared against this prediction to determine if the experience was better than expected or worse than expected. This comparison between the observed and expected outcome results in a "prediction error" signal that is used to update value representations. Neural recordings in animal models have revealed that the phasic firing of dopamine neurons, and subsequent release of dopamine in the ventral striatum, follow a pattern consistent with trial-by trial encoding of a prediction error signal that can be used for this adaptive learning process (Schultz et al., 1997, O'Doherty et al., 2003).

The dopaminergic mechanism of reinforcement learning has also been demonstrated in humans through a collection of neuroimaging and pharmacological studies (O'Doherty et al., 2003, Pessiglione et al., 2006, Yacubian et al., 2006). For example, pharmacological increases in dopamine levels led to improved learning from monetary rewards in a reinforcement learning paradigm, while pharmacological blockade of dopamine D2 receptors led to diminished learning from such incentives. Interestingly, neither of these drug manipulations lead to observable changes in learning from monetary losses (Pessiglione et al., 2006). This would suggest a dissociable involvement in the dopamine system for modulating reinforcement learning from rewards but not losses (Pessiglione et al., 2006, Yacubian et al., 2006).

Such dopamine-specific evidence is especially relevant in the context of sleep deprivation, since significant decreases in the availability of dopamine D2/D3 receptors have been reported in humans when sleep deprived using PET radioligand experiments (Volkow et al., 2008, Volkow et al., 2012). Together with the findings that gain-based reinforcement learning is diminished with pharmacological blockade of D2 receptors (Pessiglione et al., 2006), such data leads to the hypothesis that sleep deprivation will similarly lead to deficits in reward based reinforcement learning. Furthermore, given that pharmacological blockade of D2 receptors does not disrupt learning from losses (Pessiglione et al., 2006), this would further predict a specific dissociation, such that loss-based reinforcement learning will remain intact and unaltered by the state of sleep loss.

Beyond pharmacological manipulations of reinforcing learning, neuroimaging studies have also been important for identifying regional brain networks that support such information acquisition, the findings of which have additional relevance on the context of sleep deprivation. Specifically, areas of the prefrontal cortex have been implicated in integrating reward-related feedback and coding the value signal of reinforced stimuli, particularly in the context of gains (Pasupathy and Miller, 2005, Knutson and Wimmer, 2007b, Park et al., 2010). Results from the previous chapter (using the monetary incentive delay task) demonstrate that vmPFC reactivity to monetary gain feedback is diminished by sleep deprivation, which may be a further indication of the potential for sleep deprivation to diminish the capacity to learn from monetary gain feedback.

Taken together, dopaminergic alterations as well as disrupted regional brain activity in mesolimbic regions, support the hypothesis that sleep deprivation will diminish learning from reward-based feedback, while leaving punishment-based feedback learning unaltered. The following study tested this hypothesis using a monetary reinforcement-learning paradigm that employs both gains and losses, and compares sleep deprivation to a sleep rested state.

Methods

Experiment overview: Thirty-two subjects completed a probabilistic reinforcement learning task either after a night of rested sleep (N=16; 9 female) or after a night of total sleep deprivation (N=16; 8 female). Five participants (3 rested and 2 sleep deprived) from an original thirty-seven participants were excluded from analysis because they acquired net loss earnings over the task, indicating that they did not learn the task correctly, or misunderstood the instructions. All sleep condition procedures can be found in section *IV. Common Methods*.

Probabilistic reinforcement learning task: The learning task (**Fig 4.1**) was based on a previously used paradigm known to be sensitive to dopamine manipulations (Pessiglione et al., 2006, Samanez-Larkin et al., 2008, Knutson et al., 2011). The

task included three blocks, each with thirty gain- and thirty loss-trials. On each trial (**Fig 4.1**) participants were asked to choose between one of two symbols. After this choice, feedback was provided regarding whether they won $0.50 or $0 on a gain trial, or whether they lost $0.50 or $0 on a loss trial. In each pair, one symbol resulted in winning or avoiding losing on 70% of the trials. Participants were instructed to try and win as much money as possible by learning to pick the symbol that resulted in winning money or avoiding losing money more often. Importantly, each block contained a novel set of symbols, so that learning could be assessed, anew, on each block. Trial-by-trial choices as well as reaction times were recorded for assessing behavior in this task.

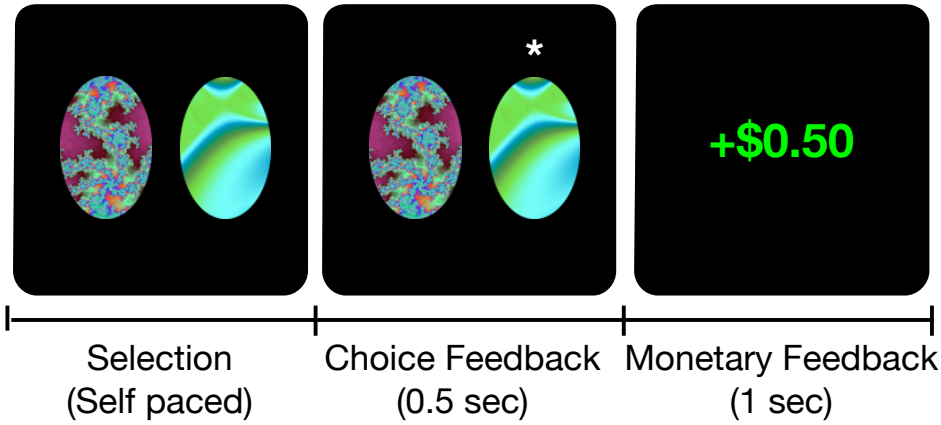

Fig 4.1) Probabilistic reward task design. Participants were first presented with a pair of cues (Selection face) and were given unlimited time to make a choice. Once the choice was selected, a star appeared above the cue to indicate the choice. Finally, monetary feedback was given at the end of the trial. A cue pair could either be associated with gaining (i.e. either winning $0.50 or $0) or with losing (i.e. either losing $0.50 or $0). Participants were instructed to try and win as much money as possible by learning the cue in each pair with either the highest probability of winning money or avoiding losing money. Cumulative winnings were reported at the end of the task and paid out in cash to the participants.

Behavioral performance analysis: Learning was assessed by plotting the percentage correct choices (i.e. choosing the symbol with a higher probability of reward) across each trial of the blocks, across subjects. A power function ($y=a*X^b$) was fit using the Matlab curve fitting toolbox to each group and conditions' learning profile in order to assess whether the learning profile was consistent with previously reported learning trajectories (Delany, 1998). Median reaction times across all trials (separately for gain and loss) were calculated for each subject and sleep group differences in these reaction times were calculated

using a t-test across subjects. Finally, total cumulative monetary winnings across reward trials, and total cumulative monetary losses across punishment trials, were evaluated (Pessiglione et al., 2006). Here, the outcomes of the first 5 trials of each block were excluded, since these trials do not contain adequate information as to the correct choice.

Results

Before comparing performance between the sleep and sleep deprivation conditions, a first analysis confirmed that the learning trajectories for each group, for both grain and loss cues, were well fit by a standard reinforcement learning power function reported in previous studies (Delany, 1998)($y=a*X^b$) (all $R^2>0.7$ & RMSE <0.08 **Fig 4.2**). Notably, in the first two gain trials the sleep rested group appears to have fortuitously picked the correct stimulus more frequently than the sleep deprived group (**Fig 4.2**), however, this percentage was not significantly different from chance for any block. Additionally, these percentages normalized between groups in the following few trials. Both groups performed well above chance (50%) for both gain and loss cues in the last ten trials of each block, when there has been sufficient time for learning (mean and (sd) reported for: Rested - Gain: 89%(15.9); Sleep Deprived - Gain: 79%(21.4); Rested - Loss: 82%(14.8); Sleep Deprived - Loss: 80%(15.6)). Thus, proficiency of

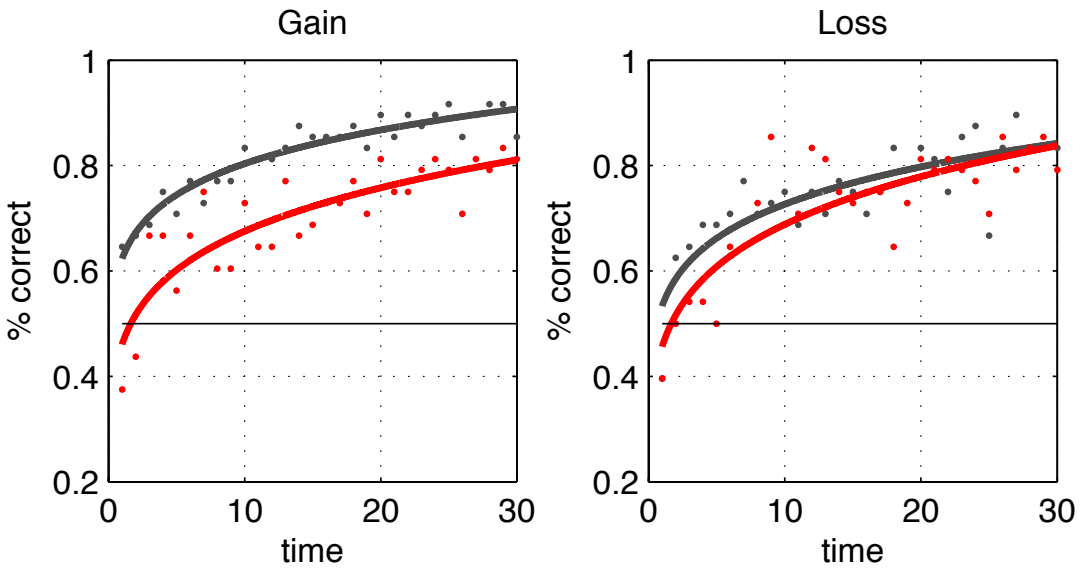

Fig 4.2) Probabilistic reward task behavior across trials. Individual dots represent averaged percentage of correct choices across subjects. Lines show best-fit power function to the group data. Red indicates sleep deprived participant group and grey represents the sleep rested group. A one-way ANOVA across the learning trials determined a significant difference between the sleep and sleep deprivation groups ($F=25.03$; $p<0.001$) for gain based learning (left), yet no such significant difference was observed (right) for learning from loss-based feedback ($F=1.18$; $p=0.28$).

reinforcement learning was expressed in both groups, for gain and loss cues.

Next, percent correct performance across trials was compared between the sleep groups and incentive conditions. **Fig 4.3** shows average performance over each third of the task (first 10 trials; middle 10 trials; last 10 trials) for rested (grey) and deprived groups for gain (A) and loss (b). For each set of ten trials an ANOVA was used to test for interactions between sleep groups and incentive conditions. This revealed a statistical trend level interaction for sleep by incentive type in the middle set of trials ($F_{1,30}$ =3.05; p=0.09) but not for the first ten trials ($F_{1,30}$=0.65, p=0.54) or the last ten trials ($F_{1,30}$ =1.82; p=0.19). In addition to correct performance, cumulative monetary earnings (from gain) and retention (from loss) over the learning session were also assessed as in previous reports (Pessiglione et al., 2006). Here, an additional ANOVA verified a significant group (sleep rested or deprived) by reinforcement cue type (gain or loss) interaction ($F_{1,30}$=5.07; p=0.03; **Fig 4.4**). Post-hoc tests revealed that, consistent with the original prediction, this interaction was driven by the sleep deprived group gaining less money on reward trials compared to the rested group, though this was a statistical trend (p=0.07), yet not suffering any greater debt across the loss trials (p=0.53). These data provide a direct test of the relative deficit of the sleep deprived group to earn money from gain trials relative to the lack of a deficit in losing money over loss trials.

Performance was also compared for gain and loss separately, in order to determine the impact of sleep deprivation. This was tested using a one-way ANOVA across all the learning trials, between the two sleep groups. Consistent with the original hypothesis, a significant difference across reinforcement learning from reward was observed between the sleep and sleep deprivation groups

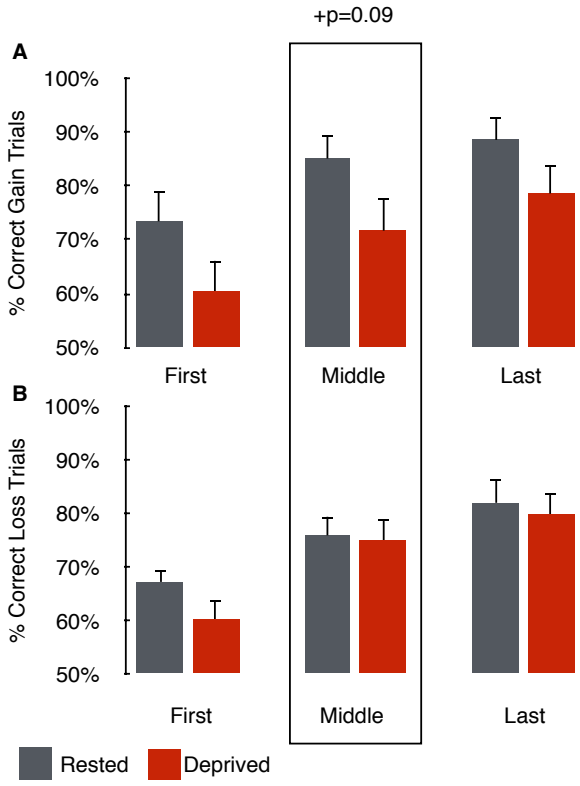

Fig 4.3) Bars represent percentage of correct stimulus choices across subjects for sleep rested (grey) and sleep deprived (red) groups. The trials are grouped in blocks of ten trials during the first, middle and last stages of the task. An ANOVA verified a statistical trend level group (sleep rested or deprived) by reinforcement cue type (gain or loss) interaction ($F_{1,30}$ =3.05; p=0.09) for the middle section of trials.

($F_{1,58}$=25.03; p<0.001), yet no such significant difference was observed for learning from loss cues ($F_{1,58}$=1.18; p=0.28). Similarly, for reaction time, sleep deprived subjects had significantly slowed reaction times across reinforcement learning from rewards, relative to sleep rested subjects (T=2.62; p=0.02), and not during learning from losses (T=1.26; p=0.22). This pattern of results reveals that while performance and reaction times related to gain learning are impaired under conditions of sleep deprivation, loss learning was not significantly impoverished, suggesting selective learning deficits and preservation, respectively.

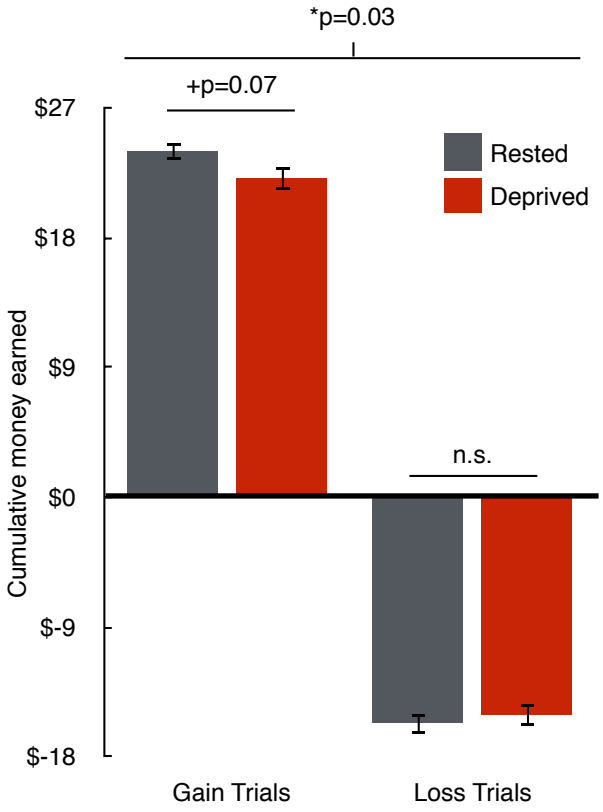

Fig 4.4) Bars represent cumulative winnings over the last 25 trials of each block for sleep rested participants (grey) and sleep deprived participants (red). An ANOVA verified a significant group (sleep rested or deprived) by reinforcement cue type (gain or loss) interaction (F=5.07; p=0.03). Post-hoc tests revealed that this interaction was driven by the sleep deprived group gaining less money on reward trials compared to the rested group, though this was a statistical trend (p=0.07), yet not suffering any greater debt across the loss trials (p=0.53).

Discussion

Consistent with the experimental hypothesis, these results established a dissociable deficit in reinforcement learning under conditions of sleep loss. Specifically, they demonstrate an impaired ability to learn from monetarily rewarding feedback under sleep deprivation, yet a preserved capacity to learn from monetary punishments. Importantly, the relatively preserved learning from monetary punishment following a lack of sleep suggests that the impairments in learning from monetary gain is unlikely due to a general cognitive deficit (e.g. alterations in working memory or attention), but rather, a selective reward-related learning deficiency.

Building on known alterations in dopamine function caused by sleep loss (Volkow et al., 2012), these finding lead to a theoretical model in which sleep deprivation causally induces a decrease in dopamine D2 receptors, which, in turn, causally disrupts reward-based reinforcement learning. Thus, dopamine may modulate the relationship between

sleep deprivation and disrupted gain (but not loss) reinforcement learning. Although it is known that sleep deprivation induces reductions in D2 receptor sensitivity, it has been unclear whether this reduction is enough to be behaviorally relevant. While the data presented here are consistent with this model, and offer a potential resulting behavioral deficit, future research measuring direct effects of sleep deprivation on dopamine processing and reinforcement learning would be needed to verify this prediction. For example, an important follow-up experiment might be to pharmacologically increase sensitivity of dopamine D2 receptors under sleep deprivation and determine if this rescues the gain feedback leading. It is important to note that while there is evidence of involvement of both D1-like and D2-like receptor involvement in reinforcement learning, here we focus on the role of D2 receptors due to the combined evidence from sleep deprivation as well as pharmacological studies which is absent for D1 receptors.

Characteristics of reinforcement learning behavior have also been shown to be affected in addiction disorders (Maia and Frank, 2011). While the connection between sleep disruption and addiction disorders as well as substance abuse is broadly recognized (Perogamvros and Schwartz, 2012), the mechanisms underlying these interactions remain poorly understood. Based on findings described earlier, one potential candidate bridging these reciprocal interactions is the link between sleep loss and D2/D3 receptor down regulation (Volkow et al., 2012). Reductions in D2/D3 receptors in the striatum are common across many substance use disorders (Volkow et al., 2007). Moreover, this functional change has been linked to the transfer from casual substance use to compulsive substance use (Volkow et al., 2007). The data described here is in line with a behavioral functional cause of decreased D2 receptor stimulation that may suggest a role in sleep deprivation in facilitating addictive behaviors.

The dissociation reported here between the impacts of sleep deprivation on gain learning and loss learning may have important implications for real world financial decision making for sleep deprived individuals. Previous reports have shown that performance on such gain- and loss-learning tasks correlate with real world asset and debt accruement respectively over the lifespan (Knutson et al., 2011). Specifically, individuals who performed poorly on laboratory measures of gain-based reinforcement learning had reduced real world assets, while individuals who performed poorly on loss based reinforcement learning were more likely to carry significant debt, defined by credit reports (Knutson et al., 2011). Based on the observed disruption in gain based reinforcement learning under sleep deprivation, one intriguing speculation is that, over time, chronic sleep deprivation may lead to an incremental reduction in financial assets due to the mechanism described by the current findings. Important economic implications additional emerge from such findings, considering increased need for retirement savings (Bloom BE, 2003). This may be particularly relevant for, and explanatory of, low-

income populations, since recent evidence has established that these same populations have less total sleep and lower sleep quality relative to higher income populations (Okun et al., 2014, Wilson et al., 2014).

In summary, the data presented here build on previous reports of brain-reward system dysfunction associated with sleep loss, extending them by establishing ecologically relevant deficits in incentive learning behavior with potential real world clinical and financial consequences.

Chapter 5

The relationship between REM sleep physiology and next day neural response to monetary reward anticipation

Introduction

The mesolimbic reward system governs a range of survival-motivated functions and supports goal directed behaviors (Haber and Knutson, 2010, Perogamvros and Schwartz, 2012). At the same time, dysfunction of this system can lead to deleterious and even life-threatening conditions including substance abuse, impulsive risk-taking and uncontrolled thrill seeking. Recent evidence has uncovered a critical interaction between sleep and these brain functions as evidence by disruption of these neural systems due to sleep deprivation. However, beyond investigations into the role of sleep deprivation on neural and behavioral reward processing, it is also important to consider the possible benefits of sleep, when it is achieved, on neural systems supporting reward processing. Doing so can help shed light on the specific elements and physiogical properties of sleep that selectively support proper reward system function. Thus, highlighting potential areas of therapeutic intervention with specific sleep targets.

To date a circumscribed number of studies have begun investigating the beneficial effects of sleep (when it is obtained) on reward-associated functions. This research can be grouped in two general areas: 1) positive emotional processing, and 2) reward-related memory. Research supporting beneficial effects of sleep on positive emotional processing has demonstrated that sleep length predicts daily variations in positive mood (de Wild-Hartmann et al., 2013). Moreover, the presence of a daytime nap, and expressly on containing REM sleep, can enhance perceived happiness of happy face stimuli (Gujar et al., 2011a). Beyond these studies on positive emotion, sleep can preferentially support the consolidation of highly rewarded information (as opposed to non-rewarded or low-reward information). This has been shown for both procedural skill memory (Fischer and Born, 2009) and declarative memory (Oudiette et al., 2013). For the latter, the amount of REM sleep attained once again predicted the degree of reward biased memory recall (Oudiette et al., 2013). Taken together, these data suggests a role of sleep, and particularly REM sleep, in supporting optimal next day reward processing within specific incentive circuits of the brain.

Evidence has further implicated an important interaction during sleep with the dopamine system, specifically REM sleep. For example, dopamine neurons in the brainstem exhibit burst firing during the onset and maintenance of REM sleep, resulting in a high release of dopamine into the striatum during REM sleep (Dahan et al., 2007). Furthermore, this dopaminergic activity has been shown to be part of the neural mechanism for transitioning to and maintaining the REM sleep state (Dahan et al., 2007), without which REM sleep becomes dysregulated. While this effect of dopamine on sleep regulation is clear, the

functional benefit of such REM-sleep regulation of mesolimbic dopamine on next-day waking dopamine and/or reward brain processing is unknown.

Considering that dopaminergic processing during sleep and during wake are unlikely to be independent in individuals, it is therefore beneficial to study the relationships between sleep physiology and waking reward processing to gain better insight into the dopamine system as well as the purpose of sleep. Furthermore, pinpointing physiological processes of sleep that specifically serve reward functions will be critical from a therapeutic standpoint because it will provide researchers and clinicians with direct sleep targets that can potentially be manipulated (either pharmacologically or behaviorally) for optimal therapeutic benefit.

Characterizing such function(s) has the potential to inform clinical disorders, most notable Parkinson's disease development, where sleep disruption is highly comorbid (estimates range from 24%-98%) (Porter et al., 2008). REM sleep problems also often precede the development of Parkinson's disease. For example, 50% of middle-aged individuals expressing REM sleep behavioral disorders (which is thought to be pathologically linked to the dopamine system), go on to develop Parkinson's disease within 16 years of the original diagnosis, and 81% developed some form of dementia within this time period (Schenck et al., 2013). Furthermore, older adult males (age 71-93) with excessive daytime sleepiness are more likely to develop Parkinson's than match controls without daytime sleepiness (Abbott et al., 2005). Nevertheless, it remains unclear whether these early sleep problems are an epiphenomenon of early sub-clinical deterioration of the dopamine system or whether such sleep disruption contributes to the development of the disease (and would therefore be a target for intervention).

Although the state of REM sleep stage has been linked to optimal functioning of the dopaminergic reward system, it is qualitatively less clear what electrophysiological properties of this REM sleep are involved in such regulation. Two spectral EEG bands represent potential candidates: 1) theta (~4-8Hz) power, and 2) beta (~18-35Hz) power. Theta band power, particularly at frontal electrode sites, has been linked to reward prediction errors as well as Pavlovian conditioning during task related waking behavior (Cavanagh et al., 2010, Cavanagh et al., 2013). Furthermore, specifically during REM sleep, theta band activity has been linked to the consolidation of negative emotional memories and amygdala responsivity (Nishida et al., 2009, Popa et al., 2010) which could potentially reflect an emotional arousal signal common to reward processing. Alternatively, beta band activity has been more specifically linked to dopamine and reward processing. Specifically, beta band power increases as neuro-degeneration of the dopamine system develops during Parkinson's disease (Delong and Factor, 2008, McCarthy et al., 2011). Furthermore, beta power

decreased with anticipation of higher rewards during an EEG monitored cued incentive experiment (Donamayor et al., 2012). These data therefore indicate that increasing theta band power or decreasing beta band power during REM sleep represent dopamine-sensitive *a priori* candidates that may accurately predict reward-dependent brain activity the next-day.

Here, we seek to address this unresolved question by investigating how individual differences in sleep physiology (using EEG sleep recordings) predict next-day variability in striatal reward reactivity, assessed with fMRI. Specifically, this study tests the hypothesis that the quantity and EEG spectral quality (specifically increased theta and decreased beta band power) during REM sleep determine the amount next day reward-dependent activation in the nucleus accumbens of the ventral striatum.

Methods

Study overview: Thirty healthy participants (18 female; age 20.4 +- 1.9sd) came into the sleep lab for a full night of PSG recorded (19-channel EEG) sleep (see section *IV. Common Methods*) and completed an fMRI monitored monetary incentive delay task the next morning (see section *IV. Common Methods*). The signal from the NAcc was extracted based on a meta-analysis of the monetary incentive delay task (MNI coordinates: R: 16, 20, -9; L: -10, 12, -3) (Knutson and Greer, 2008). Only the signal during the anticipation of monetary gains was used since this signal has been most robustly associated with NAcc activity and positive arousal states (Knutson and Greer, 2008). All monetary delay task procedures as well as fMRI acquisition, preprocessing and modeling procedures can be found in section *IV. Common Methods.*

Sleep Physiology: On the experimental night in the sleep rested session, polysomnography (PSG) sleep monitoring was recorded in the laboratory using 19-channel electroencephalography (EEG) (locations according to international 10-20 system), together with electro-oculography (EOG) at right and left outer canthi and electromyography (EMG) via three chin electrodes (Klem et al., 1999). Sleep-staging was performed manually in 20-sec epochs in accordance with standardized techniques (Rechtschaffen and Kales, 1968) from the C3-A2 electrode derivation. Recordings from two minutes of quite wake (with eyes closed) were averaged from before and after the sleep period and used for comparison analysis.

Following sleep scoring, full-head EEG recordings were then re-referenced to the right and left mastoids (A1 & A2) for spectral processing. EEG recording from the total dark period (the start of lights off to the end of lights on) was extracted, binned into four-sec epochs, and band pass filtered using Finite Impulse Response (FIR) filters (low-pas at 50Hz, High-pass at 0.6Hz). Then the full night

of EEG was visually inspected for artifacts (Achermann, 2009, Saletin et al., 2013) and any four-second epoch suspected to contain artifactual signal was marked and removed from later analysis. The remaining epochs were entered into a fast Fourier transform in order to filter the EEG signal into its component frequencies (Achermann, 2009). This transform was used to quantify the spectral amplitude of the EEG signal into frequency bands of interest (delta .6-4Hz, theta 4-7Hz, alpha 7-12, sigma 12-15, beta 15-35, gamma 35-45Hz). Relative power was computed by dividing the power in each band by the average power in all other bands and was used in order to correct for inter-subject variability in total spectral power (Pivik et al., 1993). Correlation analyses reported here used the natural log of this relative power in order to normalize the distribution of power values across participants(Achermann, 2009). All analyses were conducted using MATLAB (The Mathworks Inc. Natick, MA) and the EEGLAB toolbox (http://sccn.ucsd.edu/eeglab/).

Results

Sleep profiles: All participants attained a full night of sleep in the laboratory (Mean total sleep time: 8.3+-0.77 sd hrs). The percentages of sleep time spent in each sleep stage are presented in **Table 1**; values that are within expected ranges for normative sleep (Walker et al., 2002).

Table 5.1) Sleep statistics.

Stage	Minutes	% Sleep period
Wake after sleep onset	39.49 (30.0)	7.26 (5.4)
NREM Stage 1	46.17 (19.1)	8.49 (3.3)
NREM Stage 2	259.61 (43.9)	47.90 (6.2)
NREM Stage 3	40.98 (14.9)	7.72 (3.1)
NREM Stage 4	42.16 (24.8)	7.93 (4.8)
REM	109.20 (26.9)	20.16 (4.4)
Total NREM	388.91 (35.1)	72.04 (4.7)
Total Slow Wave Sleep	83.13 (33.2)	15.65 (6.7)
Total Sleep time	498.11 (46.4)	92.19 (5.3)

Data are reported in mean time (in minutes and percentage of the sleep period time) spent in each sleep stage with standard deviation in prentices. Sleep period time is defined as the time between sleep onset and the final awakening.

Sleep stage quantity and reward activation: Focusing first on REM sleep quantity, a statistically significant negative association was observed between minutes of REM sleep and next day NAcc BOLD reactivity (r=-0.4; p=0.026). This relationship was such that such that fewer minutes of REM sleep was associated with higher levels of reward reactivity (**Fig 5.1**). There was also a similar

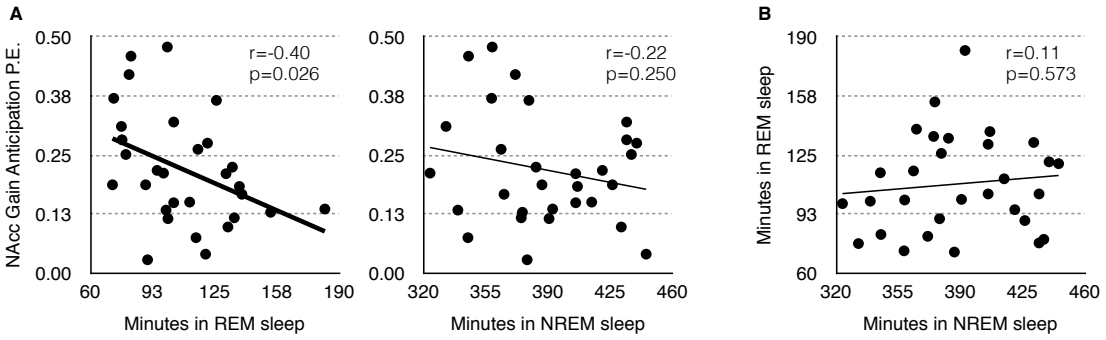

Fig 5.1) Correlation between minutes spent in REM sleep (left) as well as NREM sleep (right) with parameter estimates (P.E.) of next day NAcc reactivity to increasing monetary gains (**A**). Minutes spent in REM sleep were not significantly correlated with minutes spent in NREM sleep (**B**).

relationship between total minutes of sleep and next day NAcc reactivity (r=-0.4; p=0.029) which is not surprising given the high correlation (and dependence) between total sleep time and REM sleep (r=.66; p<0.0001). However, demonstrating specificity to REM sleep, there was no significant association between NAcc reactivity and either minutes of NREM sleep (r=-0.2; p=0.25; **Fig 5.1**) or minutes of wake after sleep onset (r=0.1, p=0.72). Additionally, in this sample minutes of REM and minutes of NREM sleep were not significantly correlated (r=0.11; p=0.57; **Fig 5.1**).

Together, these results confirm the predicted association between REM sleep quantity (amount) and next day reward reactivity, leading to the following analysis of whether the EEG spectral power *quality* of REM sleep also predicted its next day reward system activity.

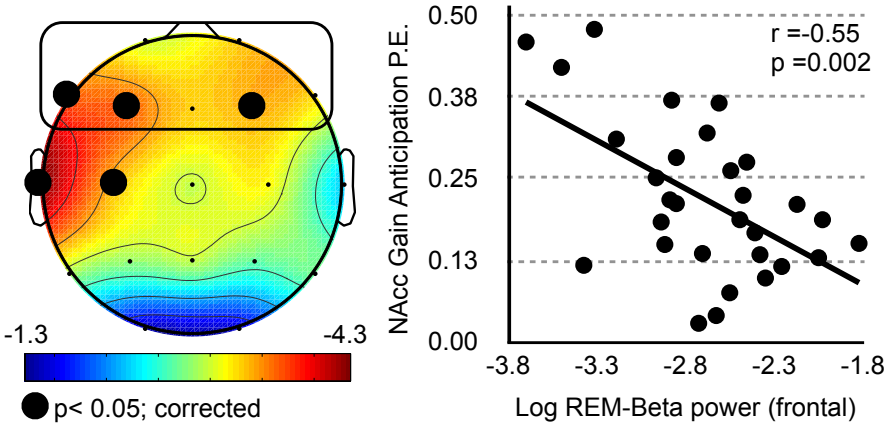

Fig 5.2) Correlations between NAcc gain anticipation reactivity and beta power during preceding REM sleep. At each electrode site (Left) and averaged frontal sites (Right).

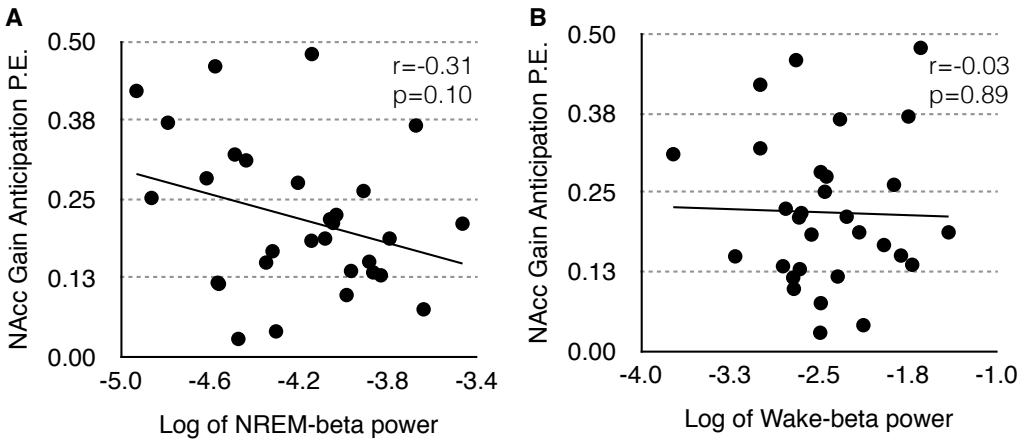

Fig 5.3) Correlations between NAcc gain anticipation reactivity and beta power during preceding NREM sleep (left) as well as resting Wake (right) averaged frontal electrode sites.

REM sleep quality and reward activation: In agreement with the hypothesis, there was a significant negative correlation between the amplitude of the average beta response during REM sleep and the next day NAcc reactivity to monetary rewards (**Fig 5.2**), averaging over the frontal electrodes of interest (Fp1, Fp2, F7, F3, Fz, F4 and F8; r=-0.55, p=0.002). A whole head analysis also confirmed significant correlations between beta power during REM sleep and next day NAcc reward responsivity at the individual electrode sites F7, F3, F4, T3 and C3 (all $p<0.05$, corrected for multiple comparison's across electrode sites). Since the time spent in REM sleep differed across participants and this difference could effect average beta-power if this power changes over the night, an additional analysis was conducted to control for time spent in REM sleep. Here, beta power from only the first hour of REM sleep for each participant was analyzed. Normalizing the time spent in REM sleep in this way did not diminish the

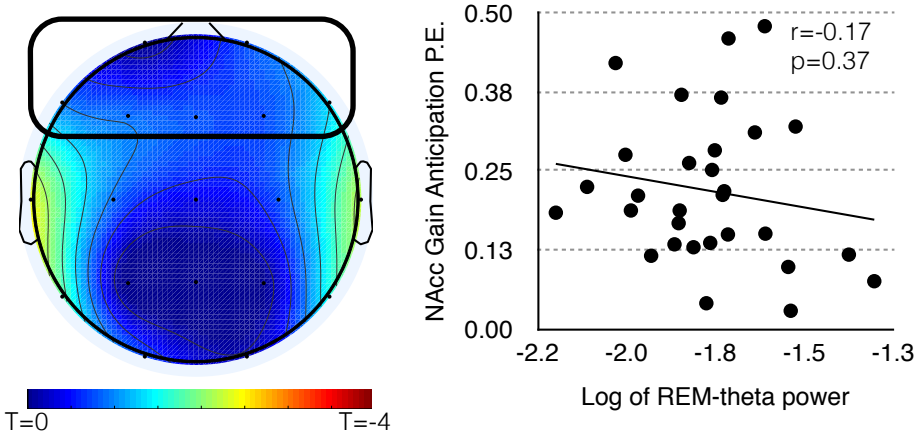

Fig 5.4) Correlations between NAcc gain anticipation reactivity and theta power during preceding REM sleep. At each electrode site (Left) and averaged frontal sites (Right).

significant correlation between beta power in the average frontal electrodes and the next day NAcc reactivity (r=-0.53, p=0.003).

In order to confirm the correlation between beta power and next day reward reactivity was specific to REM sleep, beta power during NREM sleep and during quite wake activity was also assessed. This analysis revealed no significant correlations between beta power during NREM sleep and reward reactivity at any electrode site (maximum T_{28}=-2.35; p>0.2 corrected), or averaged frontal electrode activity (T_{28}=-1.71; p=0.10; **Fig 5.3**). This was similarly true for the quite waking EEG activity (whole head maximum T_{28}=-1.62; p>0.2 corrected; averaged frontal electrode sites: T_{28}=0.03; p=0.89; **Fig 5.3**).

Counter to the experimental hypothesis, however, no correlations were observed between theta band power during REM sleep and next day NAcc reward reactivity (**Fig 5.4**) when averaged across all frontal electrodes (T_{28}=0.91; p=0.37), or at any individual electrode (maximum T28=2.43; p>0.2 corrected).

Taken together, these results indicate that beta power during REM sleep is predictive of next day NAcc reward system reactivity. Furthermore, this association is specific to REM sleep (as opposed to non-REM sleep or wake) and specific to the beta band as opposed to theta power.

Discussion

Despite rapidly accruing evidence of dopaminergic reward system activation during REM sleep, whether specific patterns of human REM sleep EEG physiology the night prior significantly predict next day reward-system reactivity has remained unknown. The current experiment addresses this question, demonstrating that inter-individual differences in next-day reward brain reactivity can be accounted for by the quantity and electrophysiological quality of REM sleep the preceding night. This qualitative correlation was specific to REM sleep, and a specific frequency band – beta power – during REM sleep, with neither NREM sleep or waking brain activity and associated EEG power activity predicting reward activity. Therefore, beta band power during REM sleep may represent a physiological individual difference marker and thus nocturnal signature of the dopaminergic mesolimbic system, that accurately predicts next day striatal reward-brain reactivity.

Several lines of evidence offer explanatory insights into this dopaminergic reward-brain association with beta power. First, beta band amplitude decreases during an incentive task as reward value increases (Donamayor et al., 2012). Second, patients with Parkinson's disease, associated with the loss of dopamine brain stem neuronal loss, express aberrantly high beta band activity (Delong and Factor, 2008, McCarthy et al., 2011). Third, beta frequency suppression is a well

characterized response to motor system activity which is also be driven by a dopaminergic network (Engel and Fries, 2010). Taken together, this evidence suggests that dopamine system activation is linked to beta EEG power in an inverse relationship, with great dopaminergic activity resulting in diminished beta EEG power. Linking this relationship to the fMRI NAcc reward reactivity measured in the current experience, BOLD fMRI responses in the NAcc during reward processing activity has also been suggested to be an indirect measure of dopamine transmission to this region (Knutson and Gibbs, 2007).

Therefore, aligning these two prior sets of literature within the context of the current findings, there are at least two theoretical frameworks which can explain these findings. First, one explanatory interpretation is that both the beta power during REM sleep and BOLD response to reward in the NAcc during wake are commonly reflecting underlying (phasic) dopamine transmission from the brainstem to the striatum in a trait-like manor. This relationship is specific to REM sleep (as opposed to wake or NREM sleep) because the phasic firing of dopamine neurons is only present during REM sleep, discussed earlier, due to its role in regulating this sleep phase (Dahan et al., 2007). A second explanatory interpretation is that beta power during REM sleep is reflective of a regulatory process of the dopamine system that occurs during sleep and determines the responsivity of the system during next day reward processing. In this way beta activity during REM sleep would be reflective of a state-like process, which regulates dopamine function on a nightly basis.

This study shows a relationship between the REM beta power physiology and the reward system reactivity during next day performance. One limitation of this study is that it is not possible to distinguish whether this relationship is reflective of trait differences in reward system activity or state specific differences whereby the sleep immediately before reward reactivity is reflective of the specific next day responding. Although not devoid of state-specific difference, previous research has indicated that the BOLD responding in the NAcc during the MID task is reflective of trait differences in reward responding (Wu et al., 2014). In this study, participants were administered the MID task with fMRI monitoring twice with an approximately one year interval in between tests and statistical analysis revealed a strong trait-like stability of responding in the NAcc. Sleep patterns and physiology have also been shown to have strong state like and trait-like qualities (Tucker et al., 2007). However, if the relationship between REM sleep physiology and reward system responding was state-like, it may have been expected that the absence of sleep (including REM sleep) reported on in **Chapter 2** would have resulted in a group shift in increased reward anticipation responding. Therefore, perhaps the most parsimonious explanation for the relationship reported here between REM beta power and NAcc reward responsivity may be that it is reflective of trait-like responding of the dopamine system during both REM sleep and reward response.

Translational implications also emerge from the hypothesis that beta power during REM sleep reflects trait differences in dopamine system activity. It can be difficult to monitor dopamine function in humans (Haber and Knutson, 2010). Thus, REM sleep beta activity may be reflective of a biomarker of dopamine activity that could be used to assess the nature and progression of dopamine-dependent diseases, most notable being Parkinson's disease. This is particularly compelling given the intimate relationship between Parkinson's disease development and sleep disruption, discussed earlier. Future research targeted at mapping the relationship between REM sleep beta power and dopamine degeneration during Parkinson's will be needed to confirm this relationship.

Finally, these results may also be informative to research into the mechanisms of major depression, where REM sleep is often excessive, both in its speed of arrival during the sleep cycle, its amount, and its intensity (Goldstein and Walker, 2014). Here we show that longer durations of REM sleep are correlated with lower next day reward reactivity. It is possible that in depression, the signature excess REM sleep may causally contribute to the well characterize diminished sense of pleasure (anhedonia) that is symptomatic of major depression, as well as blunted reward responses seen in these patient cohorts (Treadway and Zald, 2011). This is particularly intriguing given the anti-depressant effects of sleep deprivation (particularly REM sleep deprivation) that occurs in a proportion of people with depression (Clark et al., 2006), whereby the loss of REM sleep my increase the sensitivity of next-day reward systems, alleviating anhedonia.

III. General Conclusions

Overall, this report finds significant evidence supporting the overarching hypothesis that sleep deprivation would lead to dysregulation in the mesolimbic system with consequences for 1) appetitive food choices, 2) monetary incentive gain and loss sensitivity, 3) ability to learn form monetary gian and loss feedback and 4) the restorative benefit of REM sleep on next day reward processing. Beyond the discussion points described in each chapter individually, when viewed collectively two synthetic general conclusions emerge each discussed below.

First, brain processes and behaviors related to integrating information about incentives, particularly positive incentives, are uniquely detrimentally impacted by sleep deprivation. This pattern initially emerged in **Chapter 1** which showed that sleep deprivation significantly decreases activity in appetitive evaluation regions including the anterior cingulate, orbitofrontal cortex and anterior insula during food desirability choices and resulting in a higher proportion of high calorie choices. Furthermore, in **Chapter 2** sleep deprivation led to decreased reactivity in the medial prefrontal cortex to gain outcomes, which is also a region and trial period that has been linked to incentive information integration (Knutson and Wimmer, 2007b). Finally, learning about cue values in the context gains, a process dependent on integration of cue information across trials, was similarly disrupted under sleep deprivation as shown in **Chapter 4**. Importantly, all of these findings are in the context of positive incentives. However, previous reports that have shown sleep deprivation deficits using stimuli of mixed (positive and negative) incentive value and these results may also reflect failures in the system to integrate information across incentive types (Venkatraman et al., 2007b, Venkatraman et al., 2011).

Second, as hypothesized based on previous literature, dopamine signaling changes appear to be a key neural mechanism for sleep dependent changes in reward system processing. This report further supports this theory based on three key findings. First, individual differences in dopamine transporter genetics determine the interaction between sleep deprivation and reward system activation during anticipation of gains and losses (**Chapter 3**). Thus implicating trait synaptic dopamine as a key factor in determining the effect of sleep deprivation on reward anticipation. Second, as reported in **Chapter 4** reinforcement learning from monetary gain feedback (as opposed to loss) was selectively disrupted under sleep deprivation, which is the same profile seen when dopamine is pharmacologically manipulated. Third, during sleep REM sleep beta power, which is a period of sleep and a spectral band likely to reflect dopamine function, significantly predict individual differences in next day reward

anticipation reactivity in the nucleus accumbens (**Chapter 5**). Collectively, these data highlight the potential role of dopamine as a mechanism of sleep deprivation's effects on reward processing, yet they are far from conclusive. An important next step experiment might be to see if dopamine agonists (particularly D2 receptor agonists) if administered under sleep deprivation might "rescue" some of the reward system dysfunction seen under sleep deprivation, for example the ability to learn from gain feedback.

More generally, this report collectively implicates sleep (and a lack there of) in regulating mesolimbic reward system functioning, both cortically and subcortically, with resultant behavioral consequences. Considering estimates that over a third of the world's population currently fails to obtain the recommended quota of sleep, these findings become particularly relevant for understanding how sleep loss may be driving some of societies most critical decisions (e.g., financial investing, aviation, military, and medicine) as well as public health issues (e.g. obesity, addition and mental illness).

IV. Common Methods

Participants: The Institutional Review Board of the University of California, Berkeley approved the experimental protocol and we obtained written informed consent from participants. Participants were free of general medical, neurological, psychiatric or sleep disorder diagnoses and did not report any history of drug abuse or head trauma. Further, participants were free from MRI contraindications and no individuals had dietary restrictions or food allergies to any of the food stimuli.

Pre-experimental Procedures: Participants abstained from drugs, alcohol and caffeine for 3-days before each session. Participants also kept a regular sleep schedule for three days before all experimental sessions (rested and sleep deprived) in order to ensure that they were not sleep deprived coming into the study. During the regular sleep schedule participants went to bed between 10pm and 1am, slept for 7-9 hours and woke between 7am and 10am. The sleep schedule was verified using sleep diaries and wrist actigraphy. Any participants that did not adhere to these requirements were excluded from the experimental session.

Sleep Deprivation Procedures: The day of the sleep deprivation experimental session, participants were asked to wake between 7am and 10am, not to take any naps during the day and to arrive for monitoring at the lab at 9pm. This behavior was verified by self-report as well as objective wrist actigraphy (Paquet et al., 2007). Starting at 9pm participants were continually monitored over night by lab personnel. Participants were free to use their time as they wished (e.g. complete homework, watch TV, play games) but were required to remain in the experiment room and remain awake. Participants were given a small snack from 2:30am-3:00am and water ad libitum. No other food or drink was allowed during the night. All sleep deprivation sessions were separated from sleep rested sessions by at least 7 days.

Sleep monitoring and recording procedures: On the experimental night in the sleep rested session, polysomnography (PSG) sleep monitoring was recorded in the laboratory using 19-channel electroencephalography (EEG) (locations according to international 10-20 system), together with electro-oculography (EOG) at right and left outer canthi and electromyography (EMG) via three chin electrodes(Klem et al., 1999). Sleep-staging was performed in accordance with standardized techniques (Rechtschaffen and Kales, 1968) from the C3-A2 electrode derivation.

fMRI scanning Acquisition: Blood oxygenation level-dependent contrast functional images were acquired with echo-planar T2*-weighted (EPI) imaging using a Siemens 3 Tesla MRI scanner with a 12-channel head coil. Each image

volume consisted of 32 ascending 3.5mm slices (96 x 96 matrix; TR = 2000ms; TE = 28ms; voxel size 2.5 x 2.5 x 3.5 mm, FOV 224mm, flip angle = 90°). One high-resolution, T1 weighted structural scan was acquired at the end of the sleep rested session (256 x 256 matrix; TR=1900; TE = 2.52; flip angle = 9°; FOV 256mm; 1 x 1 x 1mm voxels). Concurrent eye tracking was utilized in order to further verify wakefulness.

fMRI scanning Preprocessing: Preprocessing and data analysis were performed using Statistical Parametric Mapping software implemented in Matlab (SPM8; Wellcome Department of Cognitive Neurology, London, UK). First, scan to scan variance was assessed for quality assurance using time-series difference analysis (http://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics) and individual scans with supra-threshold shifts (indicating high subject movement) were removed and replaced with the average of surrounding scans, these time-points were modeled out with dummy regressors (this affected 6 subjects total). Images were then slice time corrected, the time series was linearly detrended (Macey et al., 2004), then motion corrected, smoothed using a 6mm full-width-at-half-maximum (FWHM) Gaussian kernel and finally time-series were high pass filtered (width of 128s).

Monetary incentive delay Task: The validated monetary incentive delay (MID) task included both a gain condition (where money could be won) and loss condition (where money could be lost) associated with partially discrete neural responses (Knutson and Greer, 2008). Each trial begins with a cue indicating potential monetary gain (circle symbol) or loss (square symbol) of a certain amount of money (**Fig IV.i**), followed by an anticipatory fixation. Next, during a 2000 ms time window, a target briefly appears (180–280 ms), and participants attempt to press a button before the target is replaced by a fixation cross. Finally, Participants see theoutcome of their performance (whether they “hit” or “missed”the target) and their cumulative session earnings. The targetduration is individually set for each participant, based on a practice sessionprior to the scan, and adapted throughout the task so that the overall successrate is ~66% for each cue type. This importantly ensures that the difficulty (and end payout) is approximately equivalent across participants, and across the sleep rested and sleep deprived states. Eight cue types were used (Gain: $5, $1, $0.20, $0 and Loss: $5, $1, $0.20, $0), providing a parametric manipulation of the extent of potential gains and losses (Knutson and Greer, 2008). The value of each cue was explicitly told to the participants before the session and participants completed a short “quiz” on cue values before scanning to ensure that they understood the cue meanings. A total of 120 trials were administered in pseudorandom order, divided evenly among gain and loss trials, as well as the four incentive magnitudes.

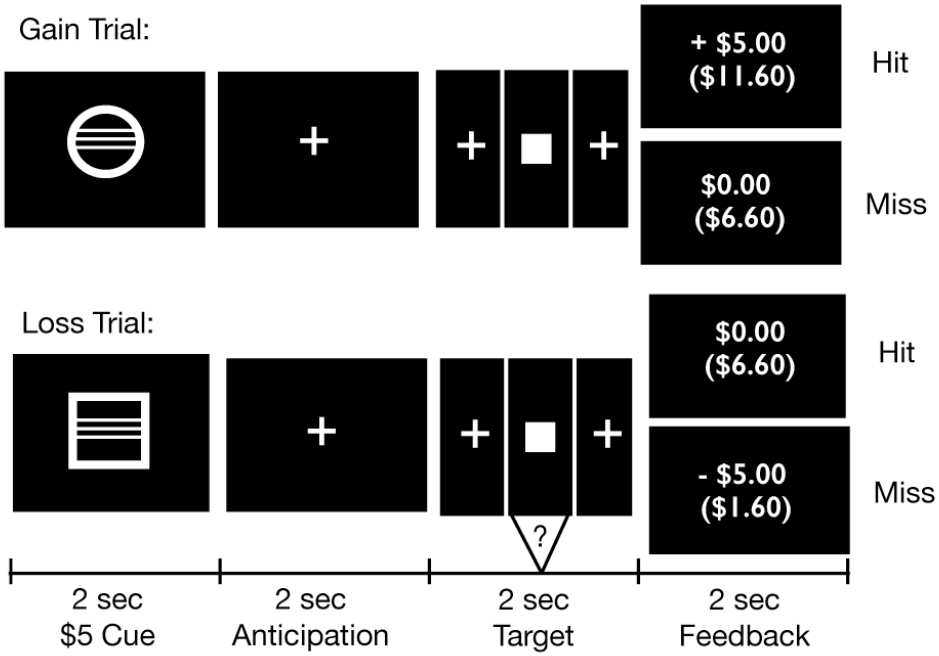

Fig IV.i) Monetary incentive delay (MID) task trials. One of eight monetary cues (gain: $0, $0.20, $1, $5; loss: $0, -$0.20, -$1, -$5) is followed by a fixation and then a jittered target presentation. The participant must respond as quickly as possible to the target in order to win (or avoid losing) the cued incentive, with outcome success signaled thereafter.

General Linear model: A separate general linear model was constructed for each subject which included 1) all gain anticipation period onsets for each trial convolved with a canonical hemodynamic response function with a 4 second duration 2) A parametric regressor of increasing reward value (for gains from $0 to $5) convolved with a canonical hemodynamic response function with a 4 second duration (this was the regressor of interest) 3) all gain outcome period onsets for each trial convolved with a canonical hemodynamic response function with a 2 second duration 4) A parametric regressor of gain trial outcomes (hits = +1; misses= -1) convolved with a canonical hemodynamic response function with a 2 second duration, 5-8) The same regressors described for 1-4 were also defined for the loss condition 9) Six movement-related covariates (three rigid-body translations and three rotations determined from the realignment preprocessing step). Separate regressors were used within the same model for each of the 2 scanner acquisition runs. All canonical hemodynamic response functions (HRF) refer to the default HRF in SPM8. First level general linear models were run on the functional scans in subject space and coordinate maps were transformed to standardized MNI space before implementation of the second level analysis.

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