NORTHWESTERN UNIVERSITY

The influence of age on the neurophysiologic and neurobehavioral response to sleep deprivation and subsequent recovery

A DISSERTATION

SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

for the degree

DOCTOR OF PHILOSOPHY

Field of Neuroscience
(Northwestern University Interdepartmental Neuroscience Program)

By

Bryce Anthony Mander

EVANSTON, ILLINOIS

December 2008

ABSTRACT

The influence of age on the neurophysiologic and neurobehavioral response to sleep deprivation and subsequent recovery

Bryce Anthony Mander

Sleep deprivation (Sd) preferentially impairs predictive and adaptive behaviors that shift responses based on the appropriate context. Behavioral studies implicate the frontal lobes as particularly susceptible to Sd. Aging also impairs frontal functioning, and alters the response to Sd. The interaction between age and Sd is poorly understood, and few studies have examined the underlying neurophysiology of this interaction. This dissertation investigates the effects of Sd on neural responses, as measured by functional magnetic resonance imaging (fMRI), associated with endogenously cued attention shifting and inhibitory control. The first study examines how Sd affects the ability to utilize predictive cues, and the second study examines the effects of Sd, age, and their interaction on brain function. Recovery from Sd is poorly understood, so the second study also examines recovery of performance and related brain activation. Recovery from Sd should be related to recovery sleep physiology, and age impacts sleep physiology. Thus, relationships between sleep physiology and daytime brain function are explored.

In study one; Sd alters how posterior cingulate and parietal activations are associated with faster attention shifts. This alteration is associated with a general change in behavioral performance in which predictive cues no longer provide a response time benefit. This suggests a change in cognitive strategy from one that utilizes cues to predict target location to one that reacts to target appearance.

In study two; we show that Sd alters how brain activation leads to successful inhibitory performance. How this functional reorganization manifests is dependent upon how tasks are performed at baseline, which is affected by age. Further, the neural response to Sd and subsequent recovery sleep is also age-dependent, and how sleep recovers next day brain activation is altered in old adults. These age-related changes in the neural response to Sd and recovery do not necessarily result in worse performance outcomes. However, future attempts to better understand, predict, and manage the effects of Sd or improve the effects of recovery sleep on daytime function will need to account for age. This is because age alters how the brain resists and recovers from sleep deprivation.

Glossary of abbreviations

Statistical
ANOVA – analysis of variance: a statistical method to compare the means of n groups taking into account the variance within each group.
CBS – cue benefit score: a calculation of the relationship between logarithmically transformed reaction times to valid and neutral cues on the Posner task.
FFT – Fast Fourier Transform: a mathematical method by which one decomposes a signal into a series of spectral components.
FWHM – full width at half maximum: an inverse measurement of RPV expressed in mm.
ICC - intraclass correlation coefficients: represents the proportion of the data that can be explained by interindividual variability.
PSTH – peri-stimulus time histogram: a histogram of the time course of the BOLD response in relation to a specific stimulus.
RPV – RESELS per voxel: a method used by statistical parametric mapping (SPM) to examine the correlation of one voxel to the next in order to determine statistical 'smoothness' of a region.
SEM – standard error of the mean
VOI – volume of interest: used to describe a predetermined region of the brain.

Neuroanatomical and neurochemical
A_1 – Adenosine type 1 receptors
ACC – anterior cingulate cortex
ACh – Aceytlcholine: a neurotransmitter.
AMPA receptors - α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors: receptors implicated in learning processes.
ARAS – ascending reticular activating system
CSF – cerebrospinal fluid
dACC – dorsal anterior cingulate cortex
DLPFC – dorsal lateral prefrontal cortex
FEF – frontal eye fields
GluR1 – Glutamate receptor subunit 1: AMPA receptor subunit.
HVc – high vocal center: part of the bird song learning system.
IPL – inferior parietal lobule
IPS – intraparietal sulcus
IVMM - intermediate ventromedial medulla
LC - locus coeruleus
LDT - laterodorsal tegmental nuclei
LPFC – left prefrontal cortex
MAO – monoamine oxidase
MnPN - median preoptic nucleus
MPB - parabrachial nucleus
mTG – middle temporal gyri

NMDA receptors - *N*-methyl *D*-aspartate receptor: receptors implicated in learning processes.
PCC – posterior cingulate cortex
PPT - pedunculopontine tegmental nuclei
RA - nucleus robustus archistriatalis: part of the bird song learning system.
RPFC – right prefrontal cortex
SCN - suprachiasmatic nucleus of the hypothalamus: the central pacemaker for circadian timing systems.
SFS – superior frontal sulcus
SLD – sublaterodorsal nucleus of the periventricular gray
TMN - tuberomammillary nucleus
VLPO - ventrolateral preoptic area
vmPFC – ventral medial prefrontal cortex

Methodological
BDI - beck depression index
BOLD - blood oxygen level dependent method: a method for using fMRI to examine relative changes in deoxyhemoglobin levels.
EEG – electroencephalography: a method used to measure gross brain activity via electrodes placed on the scalp.
EMG – electromyography: a method used to measure gross muscle activity via electrodes place on a muscle. In studies of human sleep, this placement is usually upon the chin.
EOG – electrooculography: a method to measure eye movements via electrodes placed near the eyes
ERP – evoked-related potential: an EEG measured response to a specific stimulus whether internal or external.
ESS - Epworth sleepiness scale
fMRI - Functional magnetic resonance imaging
GCRC – general clinical research center
GDS - geriatric depression scale
GFP – green florescent protein: a protein that when expressed gives off a low level of luminance. This method is often used in genetic expression experiments by attaching this protein to a target protein of interest to measure location and relative quantity of expression.
HRF – hemodynamic response function – a mathematical function that models the hemodynamic response to a stimulus.
MMSE - mini-mental state examination
MRI –magnetic resonance imaging
N350 – a negative vertex potential that occurs 350 ms following stimuli presentation during the transition into sleep.
P300 – an EEG waveform with peak positive amplitude in parietal locations that occurs 300-400 ms following stimulus presentation
P3a – the novel stimuli P300 subcomponent
P3b – the task relevant P300 subcomponent

PET - positron emission tomography
PSG – Polysomnography: a method incorporating EEG, EMG, EOG, oximetry, and a variety of methods of respiration to monitor physiological changes associated with sleep.
PSQI - Pittsburgh sleep quality index
PVT – the psychomotor vigilance task
SOA – stimulus onset asynchrony: the time delay between cue and stimulus appearance in a behavioral task.
TR – repetition time: the time interval between two 90º radio frequency waves. It is this variable that determines the time length of the MR sequence.
VBM – voxel-based morphometry: a method of determining gray and white matter density and volume using structural MRI data.

Relating to sleep and sleep loss
PGO spikes - Pontogeniculo-occipital spikes: an EEG waveform that occurs during REM sleep in cats and other mammals.
NREM – Non-rapid eye movement sleep: made up of stages 1 – 4.
REM – Rapid eye movement sleep
Sd – Sleep deprivation condition of both experiments in the present report. This is a condition where all subjects are kept awake for at least 34-36 continuous hours.
SO – Sleep opportunity condition of both experiments in the present report. This is a condition where all subjects are given the same opportunity to sleep; 8 hours in study 1, 9 hours in study 2.
SR – Sleep recovery condition in study 2 of the present report. This is a condition where all subjects are given 10 hours of time in bed to sleep following sleep deprivation.
SWA – slow wave activity: a measurement of the intensity of SWS, calculated as spectral power in the delta frequency range during SWS.
SWS – slow wave sleep: a label often given to the combine time spent in stages 3 and 4 NREM sleep.
TIB – time in bed
TRT – total recording time
TST – total sleep time
WASO - wake after sleep onset.

Other
AIM model - activation-input source-neuromodulation model: Hobson's model of states of consciousness and how it relates to states of sleep.
BOS – Bird's own song: used to describe the song of a specific bird in relation to that same bird; usually with regards to the effects of playback of its own song on brain activity and behavior.
HAROLD model – 'hemispheric asymmetry reduction in older adults' model: a model developed by Cabeza to describe the effect of aging on brain function.
HERA model – hemispheric encoding/retrieval asymmetry model: Tulving's model of prefrontal brain activation in relation to encoding and retrieval episodic memories.

LTD – Long term depression: a decrease in synaptic strength whereby the response of a neuron or group of neurons is lower upon subsequent stimulation.
LTP – Long term potentiation: an increase in synaptic strength whereby the response of a neuron or group of neurons is greater upon subsequent stimulation.
RT – reaction time

Acknowledgements

I would like to thank Dr. Lisa Wolfe, Dr. Gourineni, and Dr. Prasanth Manthena who conducted all the history and physicals for the study participants in both studies, Bryan Carter, Vijay Davuluri, Nondas Leloudas, Renata Nikolayev, Tjoson Tjoa, and the GCRC staff for their assistance in running the protocol. Vijay Davuluri deserves special credit for he collected the data for study 1. Tjoson Tjoa deserves special credit for aiding me in running the second study and interpreting the data; the study could not have been completed without his help. I would like to thank Jasmine Koita and Bonnie Hoel for their help with data analysis. I would like to thank Dr. Tobias Egner, Dr. Nancy Johnson, Dr. Marsel Mesulam, Dr. Aprajita Mohanty, Dr. Dana Small, Dr. Emily Trittschuh, and Dr. Sandra Weintraub for their advice regarding data interpretation and manuscript preparation. I would like to thank the members of my committee: Dr. Darren Gitelman, Dr. Kenneth Paller, Dr. Todd Parish, Dr. Kathryn Reid, Dr. Fred Turek, and Dr. Phyllis Zee for their thorough, thoughtful, and inspiring mentorship throughout the years. It was their guidance and support that made this project possible. I would like to thank my family and friends who supported me over the years in and out of graduate school, in particular my parents who listened to me with endless patience. Finally, I would like to thank Dr. Eve Van Cauter who taught me to believe in the importance of sleep research both for the betterment of society and for the exploration of the human condition; two of the noblest pursuits anyone could be blessed with. This research was supported by F31MH074291, Northwestern University cross-school initiative, NCRR-00048, R01 HL67604, P01 AG11412, and AG1285.

Table of Contents

General Introduction

Excessive daytime sleepiness, the inability to stay awake and alert during the major waking episodes of the day, is endemic in modern society (American Academy of Sleep Medicine, 2005). In the 2005 omnibus sleep in America poll, 50% of respondents reported "feeling tired, fatigued or not up to par during wake time at least one day a week" (National Sleep Foundation, 2005). In this same report, 37% of respondents reported that they had nodded off or fallen asleep while driving a vehicle, with 13% of them doing so at least once a month. This increased daytime sleepiness is usually caused by recurrent voluntary restriction of time allotted for sleep, or by the presence of a sleep disorder that curtails sleep or impairs sleep quality. In the 2005 omnibus sleep in America poll, only 26% of respondents reported getting the recommended 8 or more hours of sleep per night during the work week (National Sleep Foundation, 2005). This is down by almost 10% from the 1998 poll which reported 35% of respondents getting the recommended 8 or more hours of sleep during the work week (National Sleep Foundation, 2005). These data suggest that not only is sleep curtailment endemic, but that the prevalence of sleep curtailment is increasing. Perhaps as a consequence of this, the likelihood of reporting daytime tiredness and fatigue is also increasing (Bliwise, 1996). This increase in the reporting of daytime tiredness and fatigue from the 1930s to the 1980s does not appear to be due to night-time disturbances alone (Bliwise, 1996), suggesting that this daytime sleepiness may be caused by a growing trend of allotting insufficient time for sleep. In addition to this, data suggest that the prevalence of symptoms of sleep disorders may also be increasing (National Sleep Foundation, 2005).

Alongside this, the prevalence of sleep disorders increases with age (Foley et al., 1995; Monjan, 1990), and older adults generally have reduced sleep times and impaired sleep quality (Van Cauter, Leproult, & Plat, 2000). Taken together, these data suggest that sleep loss is pervasive in modern society and that the prevalence and severity of sleep loss is increasing. It is therefore important to understand the consequences of sleep loss, such as excessive daytime sleepiness, and how factors such as age interact with sleep loss to produce varied outcomes.

Sleep loss can carry with it a high economic, social, and human cost. Excessive sleepiness as a result of extended hours of wakefulness or wakefulness at the circadian nadir for alertness has been implicated to take part in multiple human error catastrophes worldwide (Mitler et al., 1988). Such catastrophes include the Three Mile Island Accident of 1979 at the Pennsylvania nuclear power plant, the nuclear plant catastrophe at Chernobyl, the Space Shuttle Challenger Accident, and the grounding of the Exxon Valdez oil tanker (Akerstedt, Fredlund, Gillberg, & Jansson, 2002; D. F. Dinges, 1995; Mitler et al., 1988). The collective effect of these particular catastrophes on society, the environment, the economy, and the lives of those involved in these catastrophes is virtually incalculable. However, when examining the economic impact of sleepiness on motor vehicle accidents, work-related accidents, home-based and public accidents, the economic cost for accidents occurring in 1988 alone was estimated to be somewhere between 43 and 56 billion dollars (Leger, 1994).

The National Highway Traffic Safety Administration (NHTSA) reported that excessive sleepiness was the principle causal factor in about 100,000 police-reported

vehicle crashes annually with a significantly elevated percentage of those resulting in serious injury or fatality in comparison to other causes (Knipling & Wang, 1994). It is widely believed that vehicle accidents go under-reported due to the difficulty involved with assessing the role of sleepiness in these accidents (D. F. Dinges, 1995; Lyznicki, Doege, Davis, & Williams, 1998; McCartt, Ribner, Pack, & Hammer, 1996; Pack et al., 1995). This difficulty exists, because there is no "breathalyzer" for sleepiness. Thus, reports of the role of sleepiness rely on the police officer's assessment of the situation; a task for which they have no adequate tool (Pack et al., 1995). Despite this complication, the effect of sleepiness on vehicle accidents is among the most studied of all sleepiness-related accidents (D. F. Dinges, 1995; J. Horne & Reyner, 1999; Lyznicki et al., 1998; McCartt et al., 1996; Mitler et al., 1988; Pack et al., 1995). These accidents are more likely to occur at night time and the early afternoon, when alertness is low (D. F. Dinges, 1995; Leger, 1994; Lyznicki et al., 1998; Mitler et al., 1988; Pack et al., 1995). They are also more likely to be single vehicle accidents that are of the "drive off the road" type (Pack et al., 1995). A survey of a random sample of New York drivers reported that 26% of respondents knew someone who had a crash due to falling asleep at the wheel or drowsiness, and a third of respondents reported they had continued to drive even when they knew they needed rest (McCartt et al., 1996). More than half of these respondents reported driving while drowsy within the last year. These data suggest that sleepiness related vehicle accidents may be much more common than currently reported.

In addition to accidents on the road, accidents in the work place have also been tied to sleepiness (Akerstedt et al., 2002; Fransen et al., 2006). An elegant study

conducted by Åkerstedt's group examined prospectively the relationship between work and health issues and fatal accidents over a span of 20 years. Specifically, sleep problems in the previous two weeks was associated with an increased risk for fatal accidents in the work place (Akerstedt et al., 2002). Another study demonstrated that symptoms of sleep disorders, sleep complaints, and excessive daytime sleepiness were associated with work injury (Fransen et al., 2006). Further, these symptoms partially explained the increased risk in shift work. Thus, the increased risk for occupational accidents in shift workers was explained by variables associated with sleepiness and poor sleep quality (Fransen et al., 2006).

Therefore, excessive sleepiness carries with it a high risk for accidents that can lead to serious injury and fatality. These accidents can affect society profoundly on an economic, social, and human scale. For these reasons, it is important to understand how sleepiness alters behavior in a way that increases the risk for accidents and catastrophes.

Sleep loss and subjective mood

Sleep loss impacts a variety of subjective measures of mood and alertness. Numerous studies of sleep deprivation and recurrent sleep restriction report increased subjective and objective sleepiness, increased general mood disturbance, increased anxiety and tension levels, decreased positive affect, increased fatigue, and even increased confusion (Angus, Heslegrave, & Myles, 1985; Blagrove, Alexander, & Horne, 1995; D. F. Dinges et al., 1997; How et al., 1994; Johnson & MacLeod, 1973; Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007; Kleitman, 1963; Meney,

Waterhouse, Atkinson, Reilly, & Davenne, 1998; Pilcher & Huffcutt, 1996; Webb & Agnew, 1974). These disturbances have usually been reported in studies using informal subject interviews or questionnaires such as the profile of mood states questionnaire (POMS) (Blagrove et al., 1995; D. F. Dinges et al., 1997; How et al., 1994; Kleitman, 1963; Meney et al., 1998). Interestingly, there is some evidence suggesting the effects of sleep loss on mood are even more dramatic than the effects on objective performance (Pilcher & Huffcutt, 1996). However, many of these reports include measurements of sleepiness and fatigue which make the interpretation of these data difficult. Specifically, does sleep deprivation cause large mood alterations, or is this primarily driven by changes in subjective sleepiness. It is most likely that the latter is the case, with moderate but clinically significant alterations in mood. Whichever are true, sleep-deprivation dependent effects on both mood and sleepiness variables are more stable within an individual across multiple sleep deprivation sessions than changes in objective performance (Lim, Choo, & Chee, 2007). And, these effects are independent of the effects of sleep loss on performance, suggesting that self-assessment of performance may be inaccurate after sleep loss (Leproult et al., 2003; Philip et al., 2004; Van Dongen, Maislin, Mullington, & Dinges, 2003).

Recently, a report examined the effects of 56 hours of continuous wakefulness on the personality assessment inventory (PAI) (Kahn-Greene et al., 2007). Following this sleep deprivation regime, subjects reported increased somatic complaints and feelings of anxiety, depression, and paranoia. Broken down more closely, somatic complaints were driven more by health concerns, anxiety more by physiological symptoms, depression

more by depressive thinking and the subjective experience of sadness, and paranoia more by feelings of persecution and resentment. These last two suggest that sleep-deprived individuals are more likely to feel mistreated and are more easily insulted (Kahn-Greene et al., 2007). These data suggest that sleep loss has a profound effect on mood which may result in maladaptive behavioral responses to the environment. A recent study by Walker and colleagues suggests that these mood alterations may be due in part to functional uncoupling between the ventral medial prefrontal cortex and the amygdala, which are regions associated with emotional regulation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). Amygdala activation was much higher after sleep deprivation in response to negative images but not to neutral images, as would be expected should ventral medial prefrontal cortex fail to modulate its activity (Ochsner, Bunge, Gross, & Gabrieli, 2002). Functional connectivity (a measure of how well correlated activity is between brain regions in the context of specific cognitive events) between the amygdala and the ventral medial prefrontal cortex was weaker after sleep deprivation, particularly with regards to the left amygdala. This is significant, as the left amygdala has been associated particularly with processing aversive stimuli and altered activity within this region has been implicated in major depression (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Lee et al., 2007). This functional uncoupling may lead to a more unstable mood state giving rise to the above described effects, with this effect being more left lateralized and thus giving rise to more negative mood effects. These effects differ from a direct effect of sleepiness, as more lateral frontal and parietal regions have been associated with subjective sleepiness changes (Chee et al., 2006; Drummond et al., 2000).

Sleep, sleep loss and objective performance

Sleep loss has a profound impact on objective performance. Probably the most well documented effect of sleep loss on objective performance is the increased occurrence of errors of omission, or "lapsing" (D. Dinges & Kribbs, 1991; Durmer & Dinges, 2005; Patrick & Gilbert, 1896; Warren & Clark, 1937). This was first reported by Patrick and Gilbert in the late 19th century (Patrick & Gilbert, 1896): "he showed a tendency to fall asleep immediately, his own will to keep awake being of no avail." These brief and uncontrollable "naps" occurred throughout the 90 hour sleep deprivation experiment; occurring even during periods of performance testing and careful subject monitoring. Indeed, one of the most dramatic effects of sleep loss is the occurrence of "hallucinations of sight" as Patrick and Gilbert refers to them (Patrick & Gilbert, 1896). These generally occurred following lapses, and over the years have been referred to as "semi-dreaming" due to the occurrence of dream-like thoughts and imagery that intrude even while the individual is awake and performing tasks (Durmer & Dinges, 2005; Kleitman, 1963). These effects of sleep deprivation have been replicated countless times over the last century (D. Dinges & Kribbs, 1991; Durmer & Dinges, 2005). The lapse effect being so robust and so well validated led to the generation of the "lapse hypothesis" by Williams and colleagues at Walter Reed Academy (Williams, Lubin, & Goodnow, 1959). Stated briefly, the lapse hypothesis suggests that sleep loss results in performance impairments that are caused by "brief periods of no response accompanied by extreme drowsiness and a decline in EEG alpha amplitude" that "increase in both

frequency and duration as sleep loss progresses" (Williams et al., 1959). After running a series of experiments, they concluded that the characteristics and magnitude of the performance impairments depended upon whether or not the task was paced by the experimenter or the subject, feedback was presented or not, motivation was high or low, and whether task duration was short or long. It appeared that task duration had a much more profound effect than either feedback or motivation. Central to their idea was that these brief periods of non-response or "naps" as Patrick and Gilbert referred to them caused "increasing unevenness of performance" (Williams et al., 1959). That is to say, performance does not globally deteriorate in a continuous fashion with increasing hours of wakefulness. In fact, performance can appear normal or near-normal at times and appear grossly impaired at others. This intermittent quality of lapsing results in increased variability in response times and accuracy on many different task designs that target a variety of cognitive domains (D. Dinges & Kribbs, 1991; Doran, Van Dongen, & Dinges, 2001; Durmer & Dinges, 2005; Kleitman, 1963; Van Dongen et al., 2003; Warren & Clark, 1937; Williams et al., 1959). Interestingly, what seems to matter most in the lapse hypothesis model is whether the task is paced by the experimenter or the subject (Williams et al., 1959). If the task is self-paced, subjects will slow down performance in order to maintain accuracy. Response times will show drastic effects but there will be little or no impact on error rate. In contrast, if the task is experimenter-paced, sleep deprivation will be more likely to result in an increased rate of errors. Predominant among these errors are errors of omission, though errors of commission also occur with increasing frequency (D. Dinges & Kribbs, 1991; Durmer & Dinges, 2005). Throughout

the literature of the next 50 years, lapses were commonly reported in studies of sleep loss and were defined as either a "non-response" or a "sufficient slowing of response time". Definitions based on response time slowing were usually in concurrence with Bills' definition which was greater than two times the mean response time (or median response time if sleep deprivation altered mean response time) (Bills, 1931; Polzella, 1975).

In order to expand on the lapse hypothesis Doran and colleagues posited their own "wake state instability" hypothesis (Doran et al., 2001). This hypothesis posits that the increased response variability following sleep deprivation is directly linked to the interaction of reciprocally inhibiting neurobiological systems that mediate wakefulness and sleep initiation. A sleep-deprived individual thus becomes unstable flipping in and out of states of sleep and wakefulness. Though conceptually identical to the lapse hypothesis, this view emphasizes that variability in responding is due to competing drives to sleep and remain alert and responding. While both of these hypotheses suggest that variability increases the longer an individual is awake, the wake state-instability hypothesis suggests that this is due to sleep-initiating mechanisms becoming more unstable with increasing hours of wakefulness (Doran et al., 2001). This hypothesis also hints that the neurobehavioral performance of sleep-deprived individuals may rely on compensatory mechanisms. These compensatory mechanisms may include behavioral strategies such as trading speed for accuracy on self-paced tasks and increasing motivational drive (Williams et al., 1959), physical strategies such as blowing cold air, turning up the radio, and walking or exercising to temporarily mask the effects of sleep loss (Angus et al., 1985; J. A. Horne & Reyner, 1995; Reyner & Horne, 1998),

pharmacological strategies such as consuming caffeine (Reyner & Horne, 1997), or neurophysiologic strategies such as the recruitment of additional neural activity to preserve performance in the face of sleep loss (Chee & Choo, 2004; Drummond et al., 2000; Drummond, Brown, Salamat, & Gillin, 2004). All of these strategies appear to have limited and short-term effectiveness with performance becoming severely impaired given enough sleep loss (Angus et al., 1985; D. F. Dinges, 1995; J. A. Horne & Reyner, 1995; Reyner & Horne, 1997, 1998; Williams et al., 1959). In the end, the best way to avoid these effects of sleep loss is to sleep long enough and well enough.

Sleep loss and attention

Though numerous studies demonstrate that sleep loss adversely affects a number of neurobehavioral domains, it has been suggested that deficits in attention underlie most if not all of the performance impairments associated with sleep deprivation (D. Dinges & Kribbs, 1991; Durmer & Dinges, 2005). Indeed, it can be argued that at least some aspect of attention is required to perform most, if not all neurobehavioral tasks. This assumption coupled with the dramatic increased occurrence of lapsing following sleep deprivation studies has led to this assertion. Data from various studies have suggested that multiple aspects of attention are affected by sleep loss independently of each other (D. Dinges & Kribbs, 1991; Gunter, van der Zande, Wiethoff, Mulder, & Mulder, 1987; McCarthy & Waters, 1997; Norton, 1970; Williams et al., 1959). What seems to be the most prominently affected is sustained attention, a term also considered synonymous with vigilance, tonic alertness, and generalized arousal (Coull, 1998; Mesulam, 1981; Oken,

Salinsky, & Elsas, 2006; Posner & Petersen, 1990). Sustained attention is often defined as the ability to maintain attention on a stimulus or series of stimuli for an extended period of time (Oken et al., 2006). Impaired sustained attention due to sleep deprivation was first characterized in Patrick and Gilbert's study in the late 19th century (Patrick & Gilbert, 1896). This was not well replicated until work by Warren and Clark in 1937 and by Bjerner in 1949 (Bjerner, 1949; Warren & Clark, 1937). Both examined the occurrence of intermittently present long pauses in responses. Bjerner's study actually linked the occurrence of impaired sustained attention with coinciding distinct electroencephalography (EEG) events (specifically alpha depression and delta intrusion) (Bjerner, 1949). This provided the first biological link between sleep-loss and impaired sustained attention. Alpha depression and delta intrusion were replicated by the Walter Reed research group further providing a biological basis for their "lapse hypothesis" (Kleitman, 1963; Williams et al., 1959). Throughout the next several decades numerous studies have replicated the observed dramatic increase in the occurrence of lapses following prolonged sleep loss. Interestingly, it wasn't until the utilization of tasks with a fast presentation rate that impairments of sustained attention were commonly observed in tasks with shorter duration (less than 10 minutes) or in total sleep loss regimes less than 45 hours. It is now known that impairments of sustained attention can be observed as early as after 20 hours of continuous wakefulness or less, and in tasks as short as 60 seconds (Angus et al., 1985; Dawson & Reid, 1997; Heslegrave & Angus, 1985; Loh, Lamond, Dorrian, Roach, & Dawson, 2004; K. Reid & Dawson, 2001). Detection of performance impairments following sleep loss on tasks as short as 60 seconds is possible

with multiple tasks (Heslegrave & Angus, 1985). It is important to note that the observation regarding 20 to 24 hours of wakefulness can be confounded by circadian variations in performance, as the circadian nadir for performance is in the early morning (Dawson & Reid, 1997; K. Reid & Dawson, 2001). Nevertheless, new sensitive tools have been developed to identify neurobehavioral performance decrements as a result of much more mild sleep loss regimes (Dawson & Reid, 1997; D. Dinges & Powell, 1985; Loh et al., 2004; K. Reid & Dawson, 2001). In particular, the psychomotor vigilance task (PVT) is widely used throughout the world to test the effects of sleep loss on performance (Thorne et al., 2005). This task is relatively simple, is apparently free of learning and aptitude effects, and is very sensitive to sleep loss, daytime dysfunction due to sleep disorders, and circadian variation in performance across the day (D. Dinges & Powell, 1985). However, it is important to note that other, similarly simple vigilance tasks have shown substantial learning curves (performance asymptote reached after 15 sessions) (Parasuraman & Giambra, 1991). For this reason, one must be skeptical of Dinges' claim of no learning effects when using the PVT in studies of sleep loss. This simple reaction time task is considered by its creators, Dinges and colleagues (D. Dinges & Powell, 1985), to be a task of sustained attention for it requires sustained focus on randomly occurring stimuli. However, it is difficult to isolate the cognitive abilities and corresponding neural networks required to perform this task and isolate which effects are most dramatically affected by sleep deprivation. The PVT task requires fixation, selective and sustained attention, visual perception, and motor response. There is no control event within the task, so isolation of specific effects of sleep deprivation on

cognitive abilities or neural networks remains impossible. However, this task does have a sustained attention component and lapsing is widely considered to be an impairment of sustained attention (Bjerner, 1949; Durmer & Dinges, 2005; Williams et al., 1959). Furthermore, the PVT is exquisitely sensitive to reaction time slowing in the face of excessive sleepiness due to its high trial density. Thus, the PVT can identify sleepiness-related performance impairments even with modest regimes of sleep deprivation or restriction, but it cannot identify how sleep loss results in these performance impairments. The PVT thus becomes a tool to detect sleepiness, not a tool to understand how sleepiness affects attention.

Recent studies have taken advantage of functional imaging techniques to study the effects of sleep deprivation on sustained attention and related neural systems (Drummond, Bischoff-Grethe et al., 2005; Drummond et al., 1999; Thomas et al., 2000; Wu et al., 1991). In the first functional imaging study of sleep loss, positron emission tomography (PET) was obtained while subjects performed the continuous performance test (Wu et al., 1991). Widespread decreases in metabolic rate were observed in the subcortical structures such as the thalamus and basal ganglia. Decreases were also observed in the frontal and temporal lobes, while an increase was observed in the parietal lobes. Interestingly sustained attention is controlled by a fronto-parieto-thalamic network (Cabeza & Nyberg, 2000; Mesulam, 1981; Posner & Petersen, 1990). Thus, these data suggested that brain activity within the attention network is altered by sleep deprivation. This presumably led to the observed performance impairments. Indeed, in this study, the amount of absolute decreases in brain metabolic rate correlated with the severity of

performance impairments (Wu et al., 1991). Almost a decade later, a second PET study of sleep deprivation was conducted (Thomas et al., 2000). The serial addition/subtraction task was performed for roughly 30 minutes after ^{18}fluorine-2-deoxyglucose (^{18}FDG) injection after waking from normal rest and after 24 hours of continuous wakefulness. In this study, they found no increases in metabolic rate following sleep deprivation. Instead, global cortical and subcortical reductions were observed with the greatest reductions being located within the frontal cortex and parietal cortex, two regions known to be associated with the control of attention. This difference in the effects of sleep deprivation on parietal cortex activation across these two PET studies is puzzling. However, these studies used different tasks and conducted their scanning at different circadian phases, which may explain the observed differences. Despite these differences, both of these studies suggest a profound effect of sleep deprivation on frontal cortex and thalamic functioning (Thomas et al., 2000; Wu et al., 1991). Another study examined the effects of sleep deprivation on the serial addition/subtraction task using the Blood Oxygen Level Dependent (BOLD) method of functional magnetic resonance imaging (fMRI) (Drummond et al., 1999). In this study, decreased activity following sleep deprivation was observed within premotor, anterior cingulate, parietal and pulvinar thalamic regions. Additionally, increased activation was observed within the right insula. However, Drummond points out quite astutely that this task is not a good task for the examination of sustained attention. It has working memory, motor, and arithmetic components. Due to the complexity of this task, use of PET methodology is limited and cannot distinguish between the effects of sleep loss on these multiple interacting domains. Nevertheless,

there are many overlaps in these studies. In particular, sleep deprivation appears to affect frontal, parietal, and thalamic functioning. The fact that these results are consistent across methodologies argues for their robust nature.

The interface between arousal and attention was examined by comparing the BOLD response to an attentional orienting task in "high arousal" (normal rest with caffeine), normal arousal (after a normal night of rest), and low arousal (after sleep deprivation) (Portas et al., 1998). The only region that seemed to vary by these conditions after comparing to a control task of passive viewing was the ventral lateral thalamus. These data are consistent with Mesulam's and Posner's models of attention, which suggests that the reticular thalamus mediates the interaction between arousal and attention (see below) (Mesulam, 1981; Posner & Petersen, 1990). Both of these models assign a critical role for the thalamus in the maintenance of sustained attention. Further evidence of an effect of sleep deprivation on sustained attention comes from the examination of the effects of sleep deprivation on the BOLD response to the PVT task (Drummond, Bischoff-Grethe et al., 2005). In this study, Drummond and colleagues regressed the fastest and slowest 10% of reaction times against the BOLD response after normal sleep and after sleep deprivation. After a normal night of sleep, the fastest responses were associated with activity within areas related to attentional and motor control (Drummond, Bischoff-Grethe et al., 2005), whereas slowest responses were associated with activity within areas related to the so called "default mode" which may reflect a disengagement from the environment (Drummond, Bischoff-Grethe et al., 2005). Following sleep deprivation, fastest responses were only associated with the motor

cortex, whereas the slowest appeared to activate this "default mode" more robustly. Interestingly, response speed by sleep condition interactions were localized to the basal ganglia and parietal and frontal regions. Due to the interaction of motor control and attention networks, these data are hard to interpret. However, the association of sleep deprivation with altered responses within the frontal and parietal regions suggests the neural control of sustained attention is affected.

Performance deficits and related physiological changes caused by sleep deprivation have also been identified in selective attention. Sleep-deprived individuals have deficits in both shifting attention towards relevant stimuli (Gunter et al., 1987; Norton, 1970) and ignoring irrelevant or potentially misleading information (McCarthy & Waters, 1997). The electrodermal orienting response to auditory stimuli, a physiological correlate of attentional and emotional processes, is delayed, shows reduced amplitude, and habituates faster following sleep deprivation (McCarthy & Waters, 1997). These findings were taken to indicate slower shifts to novel stimuli, decreased attentional allocation to stimuli, and a more rapid loss of attention to repeated stimuli respectively. In addition, event related potentials during a cueing task showed delayed latency at P255 and N350 at Cz and P3b at Pz, suggesting delayed covert orienting (Gunter et al., 1987). These studies indicate that sleep loss impairs the effective allocation of attention to relevant target stimuli, and alters physiological correlates of attention shifting. In addition, a study of divided attention compared the BOLD response to verbal learning with subtraction interference with verbal learning with counting interference (Drummond, Gillin, & Brown, 2001). The assumption in this study was that verbal

learning load would remain the same, but interference would be greater in the subtraction block. The subtraction condition would essentially be more of a strain on attentional systems than the counting condition. The hypothesis would then be that sleep deprivation impairs the ability to switch attention between subtasks. Interestingly, increased BOLD responses were observed after sleep deprivation in frontal, cingulate, and parietal regions. Indeed, the BOLD response within parietal regions correlated with preserved performance after sleep deprivation, and the BOLD response in frontal regions correlated with level of subjective sleepiness (Drummond et al., 2001). It is hard to say that these regions were related to attention per se. The simultaneous performing of multiple tasks requires a working memory component which also has dorsolateral prefrontal and parietal components (Kubler, Murphy, Kaufman, Stein, & Garavan, 2003; Wager, Jonides, & Smith, 2006). This is particularly relevant since sleep deprivation also impairs working memory and alters related parietal and prefrontal functioning (Chee & Choo, 2004; Choo, Lee, Venkatraman, Sheu, & Chee, 2005; Habeck et al., 2004). In addition, frontal components may also be described by increased difficulty on the arithmetic component of the task (Rickard et al., 2000). Thus, additional domains of attention such as selective attention, divided attention, and attentional orienting are also affected by sleep deprivation, and teasing out exactly how these parietal, frontal, thalamic, and cingulate regions are affected by sleep deprivation should be examined more closely in future studies.

These parietal, frontal, cingulate and thalamic regions have been associated with the control of attention (Cabeza & Nyberg, 2000; Corbetta, Miezin, Shulman, & Petersen,

1993; Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Mesulam, 1981; Nobre et al., 1997; Small et al., 2003). However, these regions are implicated in the control of a wide variety of attention, working memory, and inhibitory abilities (Cabeza & Nyberg, 2000; Corbetta et al., 1993; Garavan, Ross, & Stein, 1999; Kubler et al., 2003; LaBar, Gitelman, Parrish, & Mesulam, 1999). Within the attention domain, these areas have been implicated in studies of sustained attention, attentional orienting, selective attention, and divided attention (Cabeza & Nyberg, 2000). This presents with a difficult problem in interpreting exactly how sleep loss results in these attention impairments. Though tasks designed to target these attention abilities have overlapping cognitive influences, they can be accounted for in functional imaging studies with the use of careful experimental designs (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Gitelman et al., 1999). Within the attention domain, selective attention tasks may require some form of sustained attention (for one must always sustain attention upon a task), and sustained attention tasks may require some form of selective attention. Selective attention implies that attention is focused in a particular way in favor of another (Coull, 1998). To sustain attention in a particular way is to maintain attention in a particular way regardless of the environmental conditions. Additionally, both of these attentional abilities require the inhibition of other irrelevant external and internal stimuli or stimulus features, for nothing occurs in vacuum, not even a perfectly designed experiment. Thus, carefully designed experiments have become crucial. This becomes particularly important for sleep deprivation research, as sleep deprivation impairs performance on a combination of these abilities. Isolating the effects of sleep deprivation on brain-behavior relationships quickly becomes impossible

without carefully controlled experiments that carefully isolate cognitive events from each other.

In spite of the fundamental differences in experimental manipulation and conceptualization of disparate attention abilities, overlap in the neurophysiology remains. This is evident in that studies of sustained attention and selective attention identify a similar fronto-parieto-thalamic network of regions (Cabeza & Nyberg, 2000; Coull, 1998). Thus any task of one form of attention must contend with the inevitable contamination of another form of attention. Regardless of this cross modal contamination in attention studies, behavioral metrics of sustained attention and selective attention are distinct. Failure to respond and general response slowing (as per Bills' definition) are typical signs of sustained attention impairments (Bills, 1931). However, impairments of selective attention, attentional orienting, and divided attention can be measured as response speed or accuracy of one condition relative to another (Posner, 1980). Thus, sustained and selective attention can be orthogonalized by using careful experimental paradigms and behavioral metrics. It is crucial that similar methods be employed in functional imaging studies to tease apart how sleep deprivation affects these attentional specializations within this fronto-parieto-thalamic network.

Classic models of attention have been described, focusing on the contributions of these regions (along with the cingulate gyrus) to attentional control (Mesulam, 1981; Posner & Petersen, 1990). In these models a network of parietal, frontal, cingulate and subcortical structures functioned as a whole to control directed attention. In Mesulam's model, posterior parietal regions such as the intraparietal sulcus (IPS) and inferior

parietal lobule (IPL) contain sensory representations that are actively updated continuously based on the "saliency" of internal and external features (Gottlieb, Kusunoki, & Goldberg, 1998; Mesulam, 1981). Motor representations are controlled by frontal regions such as the frontal eye fields (FEF) (Mesulam, 1981; K. G. Thompson, Biscoe, & Sato, 2005). These regions are then modulated by regions that process motivational representations such as the anterior and posterior cingulate gyrus (Hopfinger et al., 2001; Mesulam, 1981; Mesulam, Nobre, Kim, Parrish, & Gitelman, 2001; Small et al., 2003). Finally, Mesulam posits that subcortical "reticular structures" modulate this entire attentional network based on the level of arousal of the individual. These reticular structures included the reticular nucleus of the thalamus, the brainstem raphe nucleus, and the locus coeruleus, which are now all associated with sleep-wake control (Mesulam, 1981; Saper, Chou, & Scammell, 2001). It is likely this interaction between reticular structures cortical regions produces the impairments observed following sleep deprivation. Additional subcortical structures, such as the pulvinar nucleus of the thalamus, the superior colliculus, and the basal forebrain are also implicated in attentional control. These regions are suggested to process sensory, motor, and motivational representations respectively, though their roles are probably more complicated (Mesulam, 1981). The basal forebrain, for example, also performs a critical role in terms of the maintenance of wakefulness (Arrigoni, Chamberlin, Saper, & McCarley, 2006). It has been posited that these "reticular structures" interact with all aspects of the attention network (Mesulam, 1981; Posner & Petersen, 1990). Indeed, neurons within disparate aspects of the ascending reticular activating system (ARAS) project not only to the

thalamus, but project diffusely throughout the entire cortex via the basal forebrain (Saper et al., 2001). Therefore, it becomes unlikely that one aspect of attention is more targeted than another. Instead, it appears that behaviors requiring prefrontal, posterior parietal, mediotemporal, and cingulate function are particularly susceptible to sleep deprivation (Mesulam, 1981; Posner & Petersen, 1990). Interestingly, these regions all act as transmodal nodes that integrate sensory information, previous knowledge, and goal-directed motor actions into conscious experience (Mesulam, 1998). It is these very same areas that are reduced during non-rapid eye movement (NREM) sleep; a state of being that is distinctly associated with loss of consciousness (Braun et al., 1997; Maquet et al., 1997; Nofzinger et al., 2002). Since these regions are implicated in a variety of cognitive abilities, and can participate in different ways depending on task context, it can be concluded that sleep deprivation will impact all abilities that rely on these brain structures. That is to say, deficits following sleep deprivation are not likely to be due solely to deficits in sustained attention. Instead, any ability requiring the functioning of these higher order transmodal nodes should be impaired by sleep deprivation. In fact, most tasks would require functioning of these regions for multiple reasons. Therefore, in order to elucidate how sleep deprivation alters brain function and leads to neurobehavioral performance impairments, carefully designed tasks, which orthogonalize different cognitive abilities from each other, are necessary. It has been postulated that prefrontal function is particularly susceptible to sleep loss (Y. Harrison & J. A. Horne, 1998; Harrison & Horne, 1999; Harrison, Horne, & Rothwell, 2000; J. A. Horne, 1988; Thomas et al., 2000). Frontal regions are important for the control of a variety of

attentional, working memory, decision-making, and response selection abilities, which are consistently impaired in sleep deprivation and restriction studies.

Sleep loss and prefrontal functioning

Mounting evidence suggests that the frontal cortex is particularly vulnerable to sleep loss. This was first noted by Piéron in his 1913 book 'Le problème physiologique du Sommeil' (Pieron, 1913). In this book he reported on a series of studies by which he deprived sleep in dogs. Of note was histological data showing degeneration within the prefrontal cortex following extended sleep loss. These data were reviewed by Howell (Howell, 1913) in a book review and again much later by Kleitman (Kleitman, 1963), but it appears these data were given little attention since. Recent evidence comes from behavioral studies that show performance impairments on tasks targeting frontal functioning (Y. Harrison & J. A. Horne, 1998; Harrison & Horne, 1999, 2000a; Harrison et al., 2000; J. A. Horne, 1988). Sleep deprivation has been shown to impair inhibitory control, decision-making, and working memory, and which are all functions regulated in large part by the prefrontal cortex (Chee & Choo, 2004; Choo et al., 2005; Chuah, Venkatraman, Dinges, & Chee, 2006; Drummond et al., 1999; Drummond, Salamat et al., 2005; Habeck et al., 2004; Y. Harrison & J. A. Horne, 1998; Harrison & Horne, 1999). These impairments then lead to thought rigidity, perseveration, and a reduced appreciation of an updated situation (Y. Harrison & J. A. Horne, 1998; Harrison & Horne, 1999, 2000a; J. A. Horne, 1988). A classic study by Horne was able to show that sleep loss impaired the ability to flexibly alter cognitive strategies to solve a problem and

the ability to generate unusual ideas (J. A. Horne, 1988). In this study, the most striking effect was perseveration of cognitive strategies even when they were not helpful. This was also shown after five days of sleep restricted to 60% of habitual amount, suggesting that recurrent sleep restriction impairs flexible thinking in a similar fashion as acute total sleep deprivation (Herscovitch, Stuss, & Broughton, 1980). Additional studies have confirmed that a variety of inhibitory-related abilities are particularly impaired by sleep loss (Chuah et al., 2006; Drummond, Meloy, Yanagi, Orff, & Brown, 2005; Y. Harrison & J. A. Horne, 1998; Harrison et al., 2000; Williams et al., 1959). Errors of commission, or responding when it is inappropriate, are among the most commonly reported errors following sleep loss (D. Dinges & Kribbs, 1991; Durmer & Dinges, 2005). In addition, studies suggest that the ability detect and process errors is impaired after sleep deprivation, and this is associated with reduced amplitude of the error related negativity (ERN), a component of the frontally-located event related potential, which has been mapped to the dorsal anterior cingulate (Dehaene, Posner, & Tucker, 1994; Scheffers, Humphrey, Stanny, Kramer, & Coles, 1999; Tsai, Young, Hsieh, & Lee, 2005).

A common critique of this frontal lobe sensitivity hypothesis is that most studies of frontal functioning utilize tasks that are more cognitively demanding and complex than tasks of other cognitive domains. The increased sensitivity of these experiments may then be due to the increased sustained attention or "vigilance" required to perform these cognitively demanding tasks. Addressing this critique, a sleep deprivation study by Gosselin and colleagues was able to show reduced frontal event related potential (ERP) amplitude but normal parieto-temporal ERP amplitude on a relatively simple task, the

novelty odd-ball task (Gosselin, De Koninck, & Campbell, 2005). These data suggest that frontal recruitment after sleep deprivation is particularly impaired even when performing a relatively simple task.

Imaging studies have shown decreases in frontal recruitment following sleep deprivation (Chee & Choo, 2004; Choo et al., 2005; Drummond et al., 1999; Thomas et al., 2000; Wu et al., 1991). These reductions appear to be larger than in any other region when quantified using ^{18}FDG-PET (Thomas et al., 2000). However, other studies have shown increased recruitment in the frontal cortex following sleep deprivation (Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001; Drummond, Meloy et al., 2005). This discrepancy between studies may be due to differences in task type, level of performance preservation following sleep deprivation, and locus of the frontal activity changes. In all of the studies showing decreased prefrontal recruitment, performance was impaired following sleep deprivation (Chee & Choo, 2004; Choo et al., 2005; Drummond et al., 1999; Thomas et al., 2000; Wu et al., 1991). However, most of the studies showing increased prefrontal recruitment, performance was largely unaffected by sleep deprivation (Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001). Smaller reductions in frontal recruitment following sleep deprivation during a working memory task have been associated with smaller performance decrements (Chee & Choo, 2004; Choo et al., 2005). It has thus been suggested that increased frontal recruitment can be compensatory (Drummond & Brown, 2001; Drummond et al., 2000). When compensatory recruitment of additional frontal activity fails to occur, performance decrements may then be more likely to occur. Finally, where the use of PET

methodology examines the change in metabolic activity in all task events collectively, event-related fMRI usually examines specific events where performance was successful. Thus, overall, activity could be decreased due to sleep deprivation. However, when events are successful, it may be due to increased recruitment of task-related regions. This hypothesis suggests that sleep deprivation not only impairs recruitment, but also impairs the efficiency within the regions that are recruited.

Given the prevalence of errors of commission after sleep deprivation, it is not surprising that these same frontal areas that show reduced metabolic activity following sleep deprivation are critical for maintaining inhibitory control (Aron, Monsell, Sahakian, & Robbins, 2004; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Garavan, Ross, Murphy, Roche, & Stein, 2002; Mesulam, 1986). Damage to these prefrontal areas lead to inhibitory deficits (Aron et al., 2004; Luria, 1965; Mesulam, 1986). Most functional imaging studies of inhibitory control show lateral frontal recruitment as part of a right-dominant, distributed network of lateral frontal, inferior parietal, and anterior cingulate areas (Bellgrove, Hester, & Garavan, 2004; Booth et al., 2003; Garavan et al., 2002; Garavan et al., 1999; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Rubia et al., 2001; Watanabe et al., 2002). However, the emphasis of right versus left dominance of inhibitory control depends on the type of inhibition task (Collette et al., 2001; Garavan et al., 1999; Matthews, Simmons, Arce, & Paulus, 2005; Rubia et al., 2001; Ruff, Woodward, Laurens, & Liddle, 2001). For example, the hayling task requires the inhibition of learned linguistic associations. This task is, not surprisingly, left dominant (Collette et al., 2001), whereas general motor related go-no go tasks based on perceptual

cues are typically right dominant (Garavan et al., 1999; Matthews et al., 2005). It is important to note, then, that inhibitory control is not a unitary concept, and can be used to describe many processes such as the suppression of intrusive sensory information, previously learned associations, and the suppression of inappropriate yet primed motor actions (Friedman & Miyake, 2004; Nigg, 2000). Performance on these tasks are not necessarily linked or correlated within individuals (Friedman & Miyake, 2004). Therefore, these inhibitory abilities are probably linked to distinct neural control mechanisms. Despite these differences, sleep deprivation appears to impair multiple inhibitory abilities (Drummond, Salamat et al., 2005; Y. Harrison & J. A. Horne, 1998; Harrison et al., 2000; Sagaspe et al., 2006). In spite of this, studies directly examining neurobiological correlates of these sleep loss-dependent inhibitory impairments are sparse.

In addition to impairing inhibitory ability and altering related prefrontal activation, sleep deprivation also impairs performance on tasks targeting decision-making and alters activity related to decision-making and logical reasoning (Drummond et al., 2004; Y. Harrison & J. Horne, 1998; Harrison & Horne, 1999, 2000a; J. A. Horne, 1988; Killgore, Balkin, & Wesensten, 2006; Venkatraman, Chuah, Huettel, & Chee, 2007). A series of studies by Harrison and Horne have shown that sleep deprivation appears to impair tasks that require flexible thinking, the generation of unusual ideas, and the unexpected revision of previously learned patterns of behavior (Harrison & Horne, 1999, 2000a; J. A. Horne, 1988). One of the most reliable behavioral changes following sleep deprivation in this regard was a tendency towards perseverative thinking. These data

were taken to suggest that though convergent thinking is resistant to the effects of sleep deprivation; divergent thinking abilities are particularly vulnerable (Harrison & Horne, 1999, 2000a; J. A. Horne, 1988). Using the Iowa Gambling Task, a task that targets ventral medial prefrontal functioning, one group was able to show that sleep-deprived individuals were more likely to persist in making riskier decisions even to their disadvantage (Bechara, Tranel, & Damasio, 2000; Killgore et al., 2006). This effect was more dramatic in the older adults, but only after sleep deprivation, suggesting that the sensitivity of ventral medial prefrontal functioning to sleep loss increases with age. When examining these effects using functional imaging, Chee's group discovered sleep deprivation resulted in greater activity within the nucleus accumbens associated with riskier choices and reduced activity in the insula and orbitofrontal cortex associated with losses (Venkatraman et al., 2007). These data suggest that a sleep-deprived individual will experience an elevated expectation of reward for riskier choices and will have an emotionally blunted response to losses.

In addition to alterations in decision-making, sleep deprivation alters functioning within networks associated with logical reasoning (Drummond et al., 2004). These alterations in brain function are present in spite of the absence of performance differences following sleep deprivation on tasks of logical reasoning and "convergent thinking" (Drummond et al., 2004; Harrison & Horne, 1999, 2000a; J. A. Horne, 1988). Increasing difficulty on a language-related logical reasoning task recruited a left dominant frontal-parietal-cingulate network of regions after normal sleep. Sleep deprivation resulted in greater increases in recruitment with similar levels of increased difficulty in primarily left

frontal regions. Additional left and right frontal and parietal regions that were not recruited after normal sleep were also recruited after sleep deprivation. This study was the first to demonstrate that sleep deprivation interacted with task difficulty to produce even greater compensatory responses within the prefrontal cortex. In addition, it accents, along with previous studies, the reliance of the sleepy brain on parietal functioning to compensate for sleep deprivation (Chee & Choo, 2004; Drummond & Brown, 2001; Drummond et al., 2000).

Sleep loss and memory systems: short term and working memory

A variety of memory systems appear to be affected by sleep and sleep loss. This observation was first described by Patrick and Gilbert (Patrick & Gilbert, 1896). Following 72 hours of continuous wakefulness, one subject could not commit a set of figures to memory, even after twenty minutes rehearsal: "A kind of mental lapse would constantly undo the work done" (Patrick & Gilbert, 1896). The other subjects showed dramatic slowing, though not to the same degree. Since this finding, a variety of tests of 'short term' or 'working memory' tasks, have shown deficits following sleep deprivation (Bell-McGinty et al., 2004; Chee & Choo, 2004; Chee et al., 2006; Chee & Chuah, 2007; Choo et al., 2005; D. Dinges & Kribbs, 1991; Drummond et al., 2000; Elkin & Murray, 1974; Habeck et al., 2004; Harrison & Horne, 2000b; Lim et al., 2007; Luber et al., 2008; Nilsson, Backman, & Karlsson, 1989; Polzella, 1975; Raidy & Scharff, 2005; Turner, Drummond, Salamat, & Brown, 2007; Williams, Gieseking, & Lubin, 1966). These data suggest that sleep deprivation results in impaired encoding of information into short term

memory (Elkin & Murray, 1974; Nilsson et al., 1989; Polzella, 1975). This is evidenced by increased copying errors upon initial encoding, which can be traced back to sensory registration (Elkin & Murray, 1974). However, sleep loss effects remain present even if subjects verify initial encoding by writing down each stimulus as it is presented, or if experimenters verify the absence of a lapse for each viewing (Polzella, 1975; Williams et al., 1966). Thus, others argue that sleep deprivation can impair encoding, retrieval, and memory trace formation processes in a way that is independent of sensory registration (Elkin & Murray, 1974; Nilsson et al., 1989; Williams et al., 1966). Effects of sleep deprivation on recognition memory are lesser than on free recall, and more pronounced after longer delays (20 seconds versus 2.5 seconds or immediate recall), particularly within the visual modality, suggesting that retrieval or maintenance of information within working memory is particularly vulnerable to the effects of sleep loss (Drummond et al., 2000; Elkin & Murray, 1974; Habeck et al., 2004; Raidy & Scharff, 2005; Williams et al., 1966). This effect is minimal if the subject is 'over-trained' on the stimulus, such as with face recognition, though judgments about recency of stimulus presentation were still impaired (Harrison & Horne, 2000b; Raidy & Scharff, 2005). Drummond and colleagues discovered, contrary to their predictions, that brain activity associated with recall and recognition was increased following sleep deprivation in several brain regions (Drummond et al., 2000). The degree of preserved free recall following sleep deprivation was correlated with the degree of increased parietal and temporal activation. It is easy to imagine how all these impairments and alterations in brain activation could still be related to impairments of attention. If one cannot attend to the information of interest,

one cannot encode the information. A multivariate approach suggested that performance and brain activation changes during a delayed matching to sample task following sleep deprivation were driven more by effects on visual processing and attention than on memory scanning per se (Habeck et al., 2004). This study pointed to highly consistent (17 out of 18 subjects) drops in occipital, temporal and parietal activation following sleep deprivation that they argued were more attributed to attentional impairments. However, this study examined the probe phase of their task, which contained memory scanning, binary decision, response selection, and motor output processes. It is truly a shame they did not examine effects of sleep deprivation separately on encoding, rehearsal, and retrieval processes of short-term memory. Their task was well designed for this analysis, having separated each of these events into different scans, and it would have answered the critical question: 'at what stage or stages of short term memory processing does sleep deprivation act?' Nevertheless, these data make an important point and Patrick and Gilbert themselves described the source of memory problems being that "attention could not be held upon the work" (Patrick & Gilbert, 1896). Making this distinction between working memory and attention processes could prove difficult, as they may be inter-related. Mesulam describes working memory as a 'special type of attentional process' which allows for the integration of information immediately available in the environment with information stored in memory systems by temporarily holding such information online (Mesulam, 1998). Thus, sleep loss may interfere with working memory by just interfering with the sustained and selective attention components of working memory.

It remains unclear whether only attentional components of working memory are affected by sleep deprivation or if distinct working memory processes can be affected as well. A study by Chee's group showed impaired working memory performance associated with higher working memory maintenance load (four items within working memory versus two) (Chee & Choo, 2004). Performance was not impaired during events where fewer items were maintained within working memory even though these items were actively manipulated within working memory. This was interpreted to mean that sleep deprivation had a lesser impact on more complex working memory tasks. However, it is just as easily interpreted to mean that sleep deprivation more greatly impacts maintenance of information within working memory than manipulation of information within working memory. A sleep deprivation study which independently varied these variables (load and manipulation) in a parametric fashion would be better able to interpret specifically the effects of sleep deprivation on these working memory processes. Nevertheless, associated with these events were sleep-deprivation related decreases in medial IPS activation and decreased deactivation within ventral medial prefrontal cortex (vmPFC) and posterior cingulate cortex (PCC). Decreased deactivations within the vmPFC and PCC correlated with increasing response times (Chee & Choo, 2004). These data correspond very well to Drummond's functional imaging study of the PVT (Drummond, Bischoff-Grethe et al., 2005). This suggests a shift in attentional resources to being less devoted to external events and more devoted to internal states. Interestingly, following sleep deprivation, increased thalamic and left prefrontal cortex activation was observed specifically during the manipulation condition.

Since performance was maintained in this manipulation within working memory condition, this activation was interpreted to be compensatory in nature (Chee & Choo, 2004). This increased left prefrontal cortex activation following sleep deprivation was also consistent with Drummond's study of verbal learning (Drummond et al., 2000). Though it appears that certain aspects of working memory are directly affected by sleep deprivation, Chee's experiment did not control for attentional effects that may have differed across their conditions (manipulation and maintenance) (Chee & Choo, 2004). This is a particularly important point, since these frontal, thalamic, and parietal regions (particularly the IPS) are well known to be implicated in attentional networks (see above) (Mesulam, 1981; Posner & Petersen, 1990). In further support of this, a study of recognition memory using a multivariate approach found that while sleep deprivation impaired recognition memory, the degree of impairment was associated with the degree of decreased activation within a network of early visual and attentional regions (e.g. occipital, inferior temporal, and precuneus) (Bell-McGinty et al., 2004). In an attempt to separate generic effects of sleep deprivation on brain function from effects on working memory processes, Chee's group conducted another study using an n-back task which parametrically varied working memory maintenance time (0-back, 1-back, 2-back, 3-back) (Choo et al., 2005). Generic main effects of state were observed in inferior parietal and anterior cingulate regions, consistent with other studies (Chee & Choo, 2004; Drummond, Bischoff-Grethe et al., 2005). Working memory load specific effects of sleep deprivation were localized to lateral prefrontal cortex, in regions known to be associated with working memory processes (Choo et al., 2005). Recruitment of parietal

and prefrontal regions associated with working memory performance was shown to decrease as a function of hours spent awake (Chee et al., 2006). Further, subjects that recruited these prefrontal and parietal regions to a greater extent in baseline rested conditions showed more preserved performance accuracy (Chee et al., 2006). These parietal and prefrontal changes following sleep deprivation are highly reproducible in subjects undergoing the same sleep deprivation procedure twice over the span of roughly one to four months (Lim et al., 2007). When intraclass correlation coefficients (ICC) were calculated, which represents the proportion of the data that can be explained by interindividual variability, only the parietal regions remained significant. These regions were localized to medial IPS, and correlated not with working memory performance, but response time variability changes (Lim et al., 2007). Hence, this may reflect more effects of sleep deprivation on attention rather than on working memory per se. A more recent study by the same group cleverly teased apart attention and visual short term memory capacity processes associated with the parietal lobes, and examined the effects of sleep deprivation on performance and functional activation within the parietal cortex (Chee & Chuah, 2007). The goal was to determine if the working memory deficits after sleep deprivation were due more to attention deficits or deficits in working memory processes. Visual arrays with one to eight colored squares were presented to subjects as they performed two tasks: 1) retained the number of different colors and judged whether the probe color was among them, and 2) say if a single square was present or absent within the center of the array. Since sleep deprivation affected activation in both tasks, they suggested that visual processing and attention impairments could explain the visual short

term memory deficits (Chee & Chuah, 2007). These data correspond nicely with that from Stern's group (Bell-McGinty et al., 2004; Habeck et al., 2004). A behavioral examination of these relationships used computational modeling to explore the effects of sleep deprivation on attention, working memory span, and episodic encoding processes separately (Turner et al., 2007). Though there was a significant effect on attention processes, the largest effect was on working memory span, and the smallest effect was on encoding. The change in attention span did not correlated with the change in working memory span nor the change in episodic encoding, suggesting these processes are independently affected by sleep deprivation instead of attention being the primary source of working memory deficits. Presumably, sleep deprivation impairs working memory processes directly and also indirectly through its effects on attention processes. These impairments seem to be predominately related to reductions in activity within the parietal cortex, while compensatory responses occur mostly within the prefrontal cortex.

Preserved parietal functioning and increased prefrontal functioning seem to preserve working memory performance across many studies (Bell-McGinty et al., 2004; Chee & Choo, 2004; Chee et al., 2006; Chee & Chuah, 2007; Habeck et al., 2004; Lim et al., 2007; Luber et al., 2008). Indeed, a transcranial magnetic stimulation (TMS) study using a delayed matching to sample paradigm showed that stimulation of upper left middle occipital gyrus and midline parietal cortex (as opposed to simulating a non-task related region, the lower left middle occipital gyrus) improved working memory performance but only if the subjects were sleep-deprived (Luber et al., 2008). Therefore, sleep loss impairs working memory processes related to encoding, maintenance of

information, and attention. These abilities are subserved by parietal and frontal regions which are altered by sleep deprivation. Increased frontal recruitment and decreased parietal suppression results in relatively preserved working memory performance.

Sleep and memory systems: Learning, Consolidation, and Generalization

In addition to sleep loss interfering with the ability to utilize memory systems efficiently, sleep itself appears to actively promote a variety of distinct memory functions. Over the last several decades, numerous reports in humans and animals have explored the relationship between sleep and learning and memory. Many of these studies, though not all, have been reviewed extensively (Born, Rasch, & Gais, 2006; Hobson, Pace-Schott, & Stickgold, 2000; Maquet, 2001; Margoliash, 2001, 2005; Paller & Voss, 2004; C. Smith, 1985; Stickgold, 2001; Stickgold & Walker, 2005a, 2005b; Walker & Stickgold, 2006). The association between sleep and memory is an old one, and has been attributed to such thinkers as David Hartley in 1791 (Stickgold, 2001) and Quintilian in the first century AD (Stickgold, 2005). In particular, Quintilian stated this rather directly in his chapter on memory (Quintilian, 1922):

> "It is a curious fact, of which the reason is not obvious, that the interval of a single night will greatly increase the strength of the memory, whether this be due to the fact that it has rested from the labour, the fatigue of which constituted the obstacle to success, or whether it be that the power of recollection, which is the most important element of memory, undergoes a process of ripening and maturing during the time which intervenes. Whatever the cause, things which could not be recalled on the spot are easily coordinated the next day, and time itself, which is generally accounted one of the causes of forgetfulness, as to strengthen the memory."

Though knowledge of this potential link between sleep and memory has existed for literally thousands of years, scientific inquiry into this phenomenon remained nearly absent until roughly forty years ago. Animal studies in rodents and cats were much more

prominent at first, with the bulk of them being conducted in the late 70s to early 80s (C. Smith, 1985). Results across these first animal studies were inconsistent with links between sleep and learning associated with different sleep states occurring at different times of the sleep period (C. Smith, 1985). Over all these studies, however, the most consistent sleep state that related to learning performance was paradoxical sleep (C. Smith, 1985), which is also known as rapid eye movement (REM) sleep (Jouvet, 1969).

Two main study designs were used in these studies. In the first, animals were exposed to a learning paradigm, and sleep variables were examined. The hypothesis was that if sleep and learning were linked, then exposing animals to a learning paradigm should alter sleep in some measurable way (C. Smith, 1985). Studies using enriched environment paradigms were also used to test this hypothesis (Mirmiran, van den Dungen, & Uylings, 1982; Tagney, 1973). The second design examined the effects of sleep deprivation on learning acquisition. The hypothesis was, if animals were exposed to a learning paradigm but lost the sleep that followed, learning should be impaired (C. Smith, 1985). Both of these study designs are plagued with difficulties or confounding factors. In the first, the obvious difficulty is choosing the right sleep variables. Is it slow wave sleep? Is it paradoxical sleep? Is it something else? Can these changes be measured using standard EEG methods, or do you need to conduct more sophisticated analyses, such as spectral analysis? Additionally, studies were affected by the timing of the sleep measurement (C. Smith, 1985). According to Smith and colleagues, there is a 'paradoxical sleep window' that is critical for learning, whereby effects that enhance or disrupt paradoxical sleep within this window have maximal impact on learning (C. Smith,

1985). This hypothesis was created to reconcile the contradictory findings in the literature (C. Smith, 1985). The second study design must contend with the direct effects of sleep deprivation, which can profoundly impact performance (see above). Thus, with this method, one will have difficulty reconciling whether sleep plays an active role in learning and memory or simply maintains alertness so the task can be performed. These problems made interpretation of many of these early animal studies difficult. However, in some studies, the timing of the increase in paradoxical sleep following pre-sleep training corresponded to the timing of maximal learning impairments associated with paradoxical sleep deprivation, lending evidence to this hypothesis (Butler & Smith, 1981; C. Smith, 1985; C. Smith, Young, & Young, 1980).

Within the last fifteen years, there has been an explosion of studies examining the role of sleep in learning and memory in humans (Atienza, Cantero, & Stickgold, 2004; Drosopoulos, Wagner, & Born, 2005; Fenn, Nusbaum, & Margoliash, 2003; Gais, Molle, Helms, & Born, 2002; Gais, Plihal, Wagner, & Born, 2000; Huber, Ghilardi, Massimini, & Tononi, 2004; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Kuriyama, Stickgold, & Walker, 2004; Laureys et al., 2001; Maquet, 2001; Marshall, Molle, Hallschmid, & Born, 2004; S. Mednick, Nakayama, & Stickgold, 2003; S. C. Mednick et al., 2002; Plihal & Born, 1999a, 1999b; Plihal, Pietrowsky, & Born, 1999; Rasch, Buchel, Gais, & Born, 2007; Stickgold, Fosse, & Walker, 2002; Stickgold, Hobson, Fosse, & Fosse, 2001; Stickgold, James, & Hobson, 2000; Stickgold, Malia, Maguire, Roddenberry, & O'Connor, 2000; Stickgold, Scott, Rittenhouse, & Hobson, 1999; Stickgold & Walker, 2005b; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000;

Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Walker et al., 2003; Walker & Stickgold, 2004; Walker, Stickgold, Jolesz, & Yoo, 2005). This explosion followed a study by Karni and colleagues with only six subjects (Karni et al., 1994). In this study, subjects performed a visual discrimination task, whereby they were to determine the orientation of three angled bars in a background of horizontal bars. In the experimental conditions, this screen was followed by a mask of randomly angled 'v' symbols. As one improves on the task, the duration between the mask and the stimulus presentation can get shorter, i.e. it takes less time to detect the target stimulus orientation (Karni & Sagi, 1991). A significant reduction in the minimum time required between stimulus and mask presentation was observed after a night of normal rest, but not after a similar time spent awake (Karni et al., 1994). This improvement was abolished when REM sleep was suppressed, but not when slow wave sleep (SWS) was suppressed. This study demonstrated that sleep played an active role in visual skill learning (REM sleep in particular). This was independent of circadian phase (as evidenced by the SWS and REM sleep suppression conditions), and sleep deprivation performance effects (as evidenced by the waking control in a different circadian phase).

Following the observations of Karni and colleagues, several other human studies concerning the relationship between sleep and learning were published from multiple labs, e.g. (Drosopoulos et al., 2005; Fenn et al., 2003; Fischer, Hallschmid, Elsner, & Born, 2002; Fischer, Nitschke, Melchert, Erdmann, & Born, 2005; Gais et al., 2002; Gais et al., 2000; Laureys et al., 2001; Maquet et al., 2000; Marshall, Helgadottir, Molle, & Born, 2006; Marshall et al., 2004; Plihal & Born, 1999a, 1999b; Plihal et al., 1999; Rasch

et al., 2007; Wagner, Gais, & Born, 2001; Walker & Stickgold, 2006). Stickgold's group replicated Karni's behavioral findings in a much larger study (Stickgold, James et al., 2000), but he also demonstrated that sleep-dependent performance improvement was not due to REM sleep alone, but was dependant on the amount of SWS in the first quartile of the night and REM sleep in the last quartile of the night (Stickgold, Whidbee et al., 2000). Specifically, this combination of SWS and REM sleep amount explained 80% of the inter-subject variance in visual discrimination improvement. This latter point was supported by a study conducted by Born's group (Gais et al., 2000), which showed that such improvement on visual discrimination was better after early, SWS dominated sleep; no different from the wake condition after late, REM dominated sleep alone; and best after a full night sleep. These data supported strongly Stickgold's hypothesis of a two step process that is initiated during SWS and requires follow-up REM sleep for the improvement of a visual discrimination skill (Stickgold, Whidbee et al., 2000).

Functional imaging of this behavioral effect demonstrated that activations within visual cortex, specifically V1, and occipital-temporal junction regions are greater following sleep than no sleep (Walker, Stickgold, Jolesz et al., 2005). Changes within these visual processing areas are consistent with previous reports utilizing this task (Karni, Weisberg, Lalonde, & Ungerleider, 1996). However, it is unclear whether this brain activity difference was due to the performance differences between sleep and no sleep conditions. In order to address this, Walker examined behavior retest accuracy regressed against bold responses across the entire brain in both 'sleep' and 'no sleep' conditions (Walker, Stickgold, Jolesz et al., 2005). Activations positively correlated with

retest accuracy were found bilaterally within occipital-temporal junction regions, and within inferior frontal regions in the 'sleep' condition. In contrast, in the 'no sleep' condition, positive correlations were localized to the right occipital-temporal junction region only. The interpretation was that the presence of sleep altered the relationship between task functional anatomy and performance. However, this study suffers from a few small problems. One issue is that regression analyses were not compared across conditions, thus we cannot know whether the relationship between brain activity and performance was statistically different across conditions. Further, performance relationships may not be as robust if performance improvement is not as large in the 'no sleep' group. Nevertheless, these data suggest that the addition of sleep not only improves visual discrimination performance, but alters functional activity associated with that performance. This may reflect long term consolidation-related processes that alter the functional organization of skill-related processes. In contrast with this study, another study showed that visual skill learning was due to local changes in functional connectivity within the primary visual cortex (Schwartz, Maquet, & Frith, 2002). This suggests that perhaps visual skill learning depends on both local processes within the visual cortex and down-stream reorganization of related functional networks.

Further work in Born's group suggested that different forms of memory may be dependent on different sleep processes (Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008; Drosopoulos et al., 2005; Plihal & Born, 1999a; Plihal et al., 1999; Wagner et al., 2001). Where REM appears to be necessary for improving emotional memory, implicit memory, and improvement of procedural skills, SWS enhances

declarative memory. This SWS-dependent declarative memory enhancement is abolished by elevated glucocorticoids, suggesting the inhibition of cortisol through the first period of the night is supportive of memory formation (Plihal & Born, 1999b; Plihal et al., 1999). A more recent study showed that learning paired words resulted in a significant functional relationship between the hippocampus and the medial prefrontal cortex two days later, but only if they were given sleep on the night after training (Gais et al., 2007). This relationship was still present six months later, suggesting that sleep caused a long-term change in functional connectivity. Further work showed that enhancing slow waves during SWS (particularly within the prefrontal cortex) improved hippocampal-dependent declarative memory performance (Marshall et al., 2006; Marshall et al., 2004). Additionally, if an odor cue presented during a training session was presented again specifically during SWS, then declarative memory was also enhanced (Rasch et al., 2007). This last point suggests that associations made, even out of the awareness of the subject while awake, could trigger related SWS-dependent declarative memory consolidation. These data argue for an active role for SWS in the consolidation of declarative memories. Interestingly, this was not true for procedural skill learning.

In addition to these studies, Stickgold's, Born's, and Tononi's groups were able to show sleep-dependent learning associated with developing motor skills (Fischer et al., 2002; Huber et al., 2004; Walker et al., 2002; Walker et al., 2003). This sleep-dependent learning effect was not dependent on the amount of practice-dependent learning, suggesting two different learning-related processes were involved (Walker et al., 2003). Further, while most of the improvement occurred on the first night, additional nights

granted additional performance improvements (Walker et al., 2003). Though this appears to be the case, the first night appears to be crucial for this type of procedural skill learning (Fischer et al., 2005; Stickgold, James et al., 2000).

Functional activation differences were observed when sleep after training was present versus absent, even 48 hours later, when both groups were well rested (Fischer et al., 2005). These were primarily reduced right premotor activation and increased left superior parietal activation. These changes were interpreted to reflect a decreased need for conscious self-monitoring in the case of the premotor activation, and an increased utilization of structures linked to automated skill processes in the case of the parietal activation. These functional data were almost entirely contradicted by a study by Walker and colleagues in the same year, though the protocol differed (Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Instead they found increased right premotor and hippocampal activation following sleep as opposed to wake, and decreased parietal activation. This was interpreted to support faster and more accurate motor output and decreased conscious spatial monitoring. It is unclear why these studies show such different results. The Walker study used the same task as the Fischer study, but compared 'sleep' and 'wake' conditions whereby subjects were trained in the morning and retested in the evening, and trained in the evening and retested in the morning. Though this design has circadian rhythm confounds, Fischer's design had presumably residual sleep deprivation confounds. Clearly, future more tightly controlled functional imaging studies will be needed to reconcile these differences and address more carefully the role of sleep in the neural plasticity of motor skill learning.

Though most other studies of sleep and learning and memory have emphasized the importance of SWS or REM sleep, motor skill learning was shown to depend on stage 2 sleep (Walker et al., 2002). However, in contrast, Tononi's group showed that training on a different type of motor task resulted in a local increase in slow wave activity at a site previously shown to be involved in their motor task (Huber et al., 2004). This increase was correlated with improvement on the task the next day. Thus, though sleep is associated with many disparate forms of learning and memory, the relationships appear to be complicated and very specific to the type of learning and memory involved. Another possibility is that the role of sleep in these learning paradigms is multi-faceted with a combination of sleep stages occurring in precise order resulting in the learning, memory consolidation, and the related performance improvements observed. Perhaps it is just the relative contributions of the relevant processes occurring during these different sleep stages that vary across learning paradigm. This theory would suggest that it is the repeated cycling of stage 2 through SWS through REM that would result in the most prominent sleep-related learning and memory performance improvements. If this were true, then learning improvements should increase parametrically across the night by number of sleep cycles with maximal performance occurring in the morning. Of course this theory is hard to test, as residual sleepiness would confound these results in a parametric fashion.

Where most of the above studies examined how sleep aided the improvement of specific abilities or retention of specific knowledge, another group showed that sleep also aided in the ability to generalize from that knowledge (Fenn et al., 2003). Using a

perceptual learning of synthetic speech paradigm, they were able to show that subjects who had slept following training were more accurate in terms of word recognition. This effect generalized to words the subjects had not previously heard spoken by the computer-controlled text-to-speech synthesizer. These data suggest that sleep-dependent learning processes utilize the ability to extract relevant information from previous experience and apply it in an adaptive manner to same and similar phenomena experienced in the future. Another study from Born's group was able to support this using a task of serial calculations (Wagner, Gais, Haider, Verleger, & Born, 2004). In this study, subjects were instructed to use a set of rules on a series of seven calculations. This was repeated a number of times, each with differing final answers. What was not revealed to the subjects was the presence of a hidden rule, which was that the solutions mirrored each other such that the second solution was always the same as the final solution. Roughly 1 in 5 of subjects in all the control conditions gained insight into this hidden rule, improving their performance dramatically. However, after training, in the group that slept before retest, this proportion increased to 3 in 5. Interestingly, the subjects in the sleep group that did not gain insight into this hidden rule instead significantly increased reaction times to each of the calculations. This alteration in calculation reaction time was not present in any of the wake groups. These data suggest that two, seemingly independent processes were occurring during sleep, and that these processes can improve distinct aspects of performance. One improved the ability to perform a cognitive skill, and the other extracted information that the subjects were not even consciously aware of during the training period, facilitating the generation of

adaptive insight into the problem. These distinct processes may depend on distinct sleep stages. An earlier study by Stickgold examined the effects of waking from different sleep stages on word priming (Stickgold et al., 1999). In this study, subjects who performed the task while awake or woken from NREM sleep showed the typical priming effects, whereas subjects woken from REM showed the largest priming effect with weakly associated words. These data suggest that REM sleep alters information processing. Thus, it may be REM sleep that promotes generalization and insight generation.

Much like the earlier animal experiments, a few studies in humans examined the effects of learning on night-time variables (Gais et al., 2002; Maquet et al., 2000; Stickgold, Malia et al., 2000). Subjects that practiced the game Tetris were more likely to have related dream reports within the first three minutes of sleep (Stickgold, Malia et al., 2000). This was true, even in amnesic patients that did not consciously remember playing Tetris during the day, suggesting that neurobiological correlates distinct from the hippocampus were involved in the hypnagogic replay. An hour of learning word pairs during the day resulted in a significant increase in sleep spindle density, particularly within frontal sites during the first sleep cycle (Gais et al., 2002). Animal studies suggest that sleep spindles may reflect hippocampal-neocortical dialogue which might be important for long term memory consolidation (Siapas & Wilson, 1998). These data are consistent with a rat study of hippocampal 'place cells' (Wilson & McNaughton, 1994). In this study, correlated firings between neurons while awake and moving were preserved during sleep, suggesting reactivation of neuronal populations during sleep. These correlations were stronger during synchronized bursts that occurred during NREM sleep

within the hippocampus. Maquet's group showed that premotor and occipital activations associated with performing a visuo-motor skill were reactivated during REM sleep (Maquet et al., 2000). All these data inspired the reactivation hypothesis, which suggested that sleep-dependent learning occurred due to reactivation of specific neuronal groups at night that were previously activated during the day (Maquet, 2001). This reactivation could strengthen the synapse in a Hebbian manner, such that repeated activations of the same synapse could lead to long term strengthening of synaptic weights (Hebb, 1949). This hypothesis is further evidenced by studies of genetic expression during REM sleep (Ribeiro, Goyal, Mello, & Pavlides, 1999; Ribeiro et al., 2002). In one study expression of immediate early gene zif-268, a gene associated with neuronal activity-dependent neural plasticity, was 'reinducted' during REM sleep within the hippocampus, the frontal cortex, the dentate gyrus, and the piriform cortex (Ribeiro et al., 1999). This was true if rats were exposed to an enriched environment, but not if they were exposed to a plain cage environment. Interestingly, zif-268 expression did not differ between control and enriched environment rats during wake nor during NREM sleep, and in both cases, expression of zif-268 dropped significantly during NREM sleep. In a follow up study, induction of hippocampal long-term potentiation (LTP) during wake was followed by increased zif-268 expression during REM sleep, specifically within extra-hippocampal regions such as the amygdala, entorhinal cortex, and auditory cortices (Ribeiro et al., 2002). In later REM periods, this expression reaches somatosensory and motor cortices. If hippocampal activity is blocked during REM sleep, this zif-268 expression is blocked; suggesting that zif-268 expression during REM sleep is driven by

the hippocampus. These data support the hypothesis that REM sleep is involved in the hippocampal-neocortical dialogue that consolidates memories. Thus, learning promotes changes within NREM and REM sleep, be these changes reflected in dream reports, EEG variables, metabolic neuronal activity, neuronal spiking behavior, or gene expression.

Despite the wealth of data, critics of the link between sleep and learning remain steadfast in their positions (Siegel, 2001; Vertes & Siegel, 2005). They point out the following critiques: 1) in the animal literature, the presence of a REM window is inconsistent across studies and effects on learning are inconsistent; 2) correlations between improved learning and sleep variables are inconsistent across studies; 3) reactivation may not actually relate to learning improvement; and 4) REM suppression by MAO inhibitors or brain damage does not appear to affect cognitive functioning. In their arguments, however, they make many logical fallacies, and misquote the literature quite often (Siegel, 2001; Stickgold & Walker, 2005b; Vertes & Siegel, 2005). This was quite apparent, even at the explosive debate at APSS 2003 in Chicago. The first critique is quite warranted, however it does not rule out a role for sleep in learning. One cannot prove the null hypothesis. The second critique also does not rule out a tie between sleep and learning. It just highlights how complicated the relationships might be. Just as different forms of learning require different neurobiological, neurochemical, and neuroanatomical systems, so might they require different sleep-related processes. The third critique only holds up if you cannot show that the reactivation does not predict daytime performance improvement. Work by Tononi and Born refute this (Huber et al., 2004; Marshall et al., 2006; Marshall et al., 2004). The final critique has several flaws.

One flaw is that this critique assumes that MAO inhibitors suppress all REM-related processes that might aid in learning. Processes that occur during REM may still occur despite a change in PGO spikes, neurochemical changes, and altered EEG signals. For example, specific activation of the limbic system that is greater than observed during wakefulness may still occur (Maquet et al., 1996; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997). Another flaw is that this critique assumes that REM–related learning functions could not occur during NREM sleep if REM was suppressed for a prolonged period of time. A third, major flaw is that there has been no systematic study of these patients on tasks that have been shown to require sleep-dependent learning (Stickgold & Walker, 2005b). Additionally, they also dismiss any relationship between NREM sleep and learning, with little cause, avoiding the work of Born, Tononi, and McNaughton (as well as others) in their discussion (Siegel, 2001; Stickgold & Walker, 2005b; Vertes & Siegel, 2005). Despite these critiques, as the years continue, behavioral, neurophysiological, pharmacological, and molecular (see below) evidence continues to support a link between sleep and learning and memory.

Alongside these human studies, a series of elegant studies of bird song reinforcement learning were conducted by Margoliash's lab at the University of Chicago (Dave & Margoliash, 2000; Dave, Yu, & Margoliash, 1998; Margoliash, 2001, 2005; Rauske, Shea, & Margoliash, 2003; Shea & Margoliash, 2003). Over the course of the debate between Stickgold and Smith and Seigel and Vertes, these studies were largely ignored, much to the detriment of the scientific merit of the debate (though they were mentioned in passing in these reviews (Siegel, 2001; Stickgold & Walker, 2005b)). Dan

Margoliash, who at one point described himself as 'being dragged kicking and screaming into the sleep field' by his data, presents compelling evidence in support of the role of sleep in birdsong learning and memory consolidation. The first evidence came from a study in anesthetized zebra finches (Dave et al., 1998). The bird song system involves several distinct nuclei; two prominent nuclei are the nucleus robustus archistriatalis (RA) and the sensory-motor nucleus HVc within the forebrain. Studies of these regions occurred generally in birds under anesthesia, simply for ease of experimentation. These studies showed that neurons in these regions are responsive to specific acoustic features of the birds own song (BOS), which are selective to their individual song relative to other songs (Margoliash, 1983; Margoliash & Konishi, 1985). Using a relatively new technique, whereby they recorded activity within these two regions in awake and behaving zebra finches, they discovered that, surprisingly, auditory responses within the RA neurons were lower while the bird was awake than while under anesthesia. This turns out to be true for multiple sets of neuronal populations within the RA and HVc (Rauske et al., 2003). Exploring further, they discovered that, much like under anesthesia, BOS specific auditory responses within RA neurons increased while birds were asleep. This is also true within the HVc, in which auditory responses to the BOS were ubiquitous, stronger than during waking, and selective to the BOS (with responses to conspecific song and reversed BOS resulting in marked inhibition) (Rauske et al., 2003). This effect was not limited to a particular part of the night, suggesting that this effect may not be tied to one specific sleep state. Additionally, RA neurons exhibited periodic burst firing during sleep that was similar to firing patterns observed under

anesthesia. This RA neuron burst firing was abolished when norepinephrine (NE) was injected into the HVc, but not the RA, as were auditory responses within RA neurons (Dave et al., 1998). These data suggest that the auditory responsiveness of RA motor neurons is mediated at least in part by HVc activity and is reduced by NE input, which primarily stems from the locus coeruleus, a wake promoting center (see below) (Saper et al., 2001). A similar effect was observed with acetylcholine (ACh) injection and electrical stimulation of the basal forebrain (Shea & Margoliash, 2003). This effect of electrical stimulation was blocked by injection of ACh antagonists within the HVc. HVc activity also exhibits bursts during singing and sleep in similar ways, and in both cases, activity is selective to playback of BOS (Rauske et al., 2003). Auditory feedback is required for adult zebra finches to maintain their song (Nordeen & Nordeen, 1992). These data led Margoliash to hypothesize that auditory feedback during the day altered HVc activity which would then alter RA responsiveness during sleep. In support of this, Margoliash noted that the neuronal burst firing within HVc was similar in character to that observed within hippocampal neurons by McNaughton's group (Dave et al., 1998; Wilson & McNaughton, 1994). Indeed, his hypothesis was very similar to the reactivation hypothesis.

In a follow-up study, Margoliash's group examined this hypothesis more closely (Dave & Margoliash, 2000). A critical problem in at least some forms of reinforcement learning is that some biological systems will experience a delay between premotor activity and sensory feedback. This premotor activity cannot be reinforced or 'punished' if the premotor neurons giving rise to it are already involved in another premotor task.

This is particularly true for bird song learning, which involves singing a large set of distinct syllables that occur immediately after one another completing a motif which repeats to form a song. Sleep is a potential solution, as replay of song premotor neural activity can occur throughout the song system and be independent of the actual sound production and perception. The hypothesis is that sensory information obtained during the day within the HVc could then be later delivered to RA upon reactivation of the same neuronal ensembles to reinforce the neuronal behavior in the appropriate manner. In this study, playback of the BOS while birds were asleep elicited neural firing similar in structure and timing to that observed in waking singing (Dave & Margoliash, 2000). This was true for ensembles of neurons up to 400 µm apart eliciting complex firing patterns for as long as 1 second or more, making this highly unlikely to be due to chance. Furthermore, altering the BOS replay during sleep by selectively deleting syllables altered spontaneous burst firing to syllable-specific bursts (Dave & Margoliash, 2000). This suggests that the spontaneous 'replay' was actually related specifically to the BOS. These data elegantly address the critique of Siegel and Vertes regarding the relationship between 'reactivation' and daytime activity.

Taken together, these bird song studies show that reinforcement bird song learning depends upon sleep (Dave & Margoliash, 2000; Dave et al., 1998; Margoliash, 2001, 2005; Rauske et al., 2003; Shea & Margoliash, 2003). Neurons associated with auditory feedback are more selectively active to the BOS when birds are asleep (Dave & Margoliash, 2000; Dave et al., 1998; Rauske et al., 2003; Shea & Margoliash, 2003). This responsiveness is reduced when wake promoting sites are stimulated or wake-

promoting transmitters are injected (Dave et al., 1998; Shea & Margoliash, 2003). At night, these neuronal populations reactivate as ensembles spontaneously and in a similar structure and timing as observed specifically during singing, though the birds are not singing (Dave & Margoliash, 2000). These 'replays' can be induced by playback of the BOS but not in response to other stimuli matched for loudness and complexity (Dave & Margoliash, 2000; Dave et al., 1998; Rauske et al., 2003). Selectively altering playback by deleting specific syllables of the BOS selectively alters neuronal population firing (Dave & Margoliash, 2000). Indeed, upon examination of these data, it is hard to imagine that anyone could legitimately question the validity of the claim that sleep is critical for at least some learning behaviors.

The synaptic homeostasis hypothesis, as described by Tononi, states that 1) synapses are potentiated during wakefulness, 2) homeostatic regulation of slow wave activity is tied to the amount of synaptic potentiation, 3) slow wave activity (SWA) causes global synaptic downscaling, and finally, 4) this downscaling effect contributes to memory performance through preservation of relative synaptic strengths and improvement of signal to noise ratio at the neuronal level (Tononi & Cirelli, 2003, 2006). Evidence for the first point comes from studies such as those showing that local synaptic density increases upon whisker stimulation for 24 hours, and those showing spontaneous wakefulness is associated with molecular and genetic expression changes that mark LTP induction (Cirelli, Gutierrez, & Tononi, 2004; Cirelli & Tononi, 2000; Knott, Quairiaux, Genoud, & Welker, 2002). This is further evidenced by an apparent reduction in said genetic expression during sleep (Cirelli et al., 2004; Cirelli & Tononi, 2000). The second

point is more speculative, but it can be suggested that brain regions that 'work harder' during the day should build up more of a homeostatic increase in SWA. This appears to be the case, at least with regards to practicing a visual motor skill, whereby practice during the day resulted in local increases in SWA that dissipated in a similar fashion as global SWA (Huber et al., 2004). The reverse also seems to be true, whereby arm immobilization resulted in reduced SWA within relevant arm sensory and motor regions (Huber et al., 2006). This was also accompanied by poorer performance while using the immobilized arm. Perhaps the strongest evidence for the third point comes from a recent study in rats by Tononi's group, which suggests that overall synaptic strength is increased during wakefulness and decreased following periods of sleep (Vyazovskiy, Cirelli, Pfister-Genskow, Faraguna, & Tononi, 2008). Among the best markers for long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission are the trafficking and phosphorylation and de-phosphorylation of post-synaptic glutamatergic AMPA receptors, specifically including the GluR1 subunit (Malenka & Bear, 2004). Vyazovskiy and colleagues were able to show that, within the cortex and hippocampus, wakefulness was associated with increased synaptic GluR1 levels and increased phosphorylation of GluR1 (Vyazovskiy et al., 2008). During sleep, the opposite was seen, with decreased presence of GluR1 levels and increased dephosphorylation of GluR1. Evidence for the final point comes from the same study, whereby they show that extended wakefulness can lead to partial LTP occlusion (reduced ability to establish LTP) (Vyazovskiy et al., 2008). In contrast LTP is easily induced after a period of sleep. It is further proposed that downscaling may improve performance

by improving signal to noise ratio (Tononi & Cirelli, 2003, 2006). The central tenant in this idea is that synaptic strengths associated with noise are generally represented by weaker synaptic strengths than those represented by signal. The veracity of this statement remains to be tested.

Despite these data, there are those that disagree with the synaptic homeostasis hypothesis (Born et al., 2006; Rasch et al., 2007). These critics argue that direct manipulation of SWA leads to learning improvements, initiation of sleep after learning leads to reactivation of specific neuronal groups and alters long-term network connectivity (Born et al., 2006; Rasch et al., 2007). It is likely that both of these processes are occurring, with specific localized increases in synaptic strengthening occurring over a background of global synaptic downscaling. Alternatively, these distinct processes could occur at different periods of the sleep cycle. One way to test this possibility would be to use two-photon microscopy in mice expressing green fluorescent protein (GFP) in distinct neuronal groups. This method has been used previously to examine dendritic spine formation, removal, and stabilization over the space of days or even months (Grutzendler, Kasthuri, & Gan, 2002; Trachtenberg et al., 2002). This technique appears optimal for investigating the role of sleep in neuroplasticity, as spine formation could be examined before and after periods of sleep and wakefulness. Additionally, the effects of whisker stimulation, enriched environment, and various learning paradigms could be explored before and after sleep to determine directly whether dendritic spine formation (and thus synaptogenesis) and/or spine removal occurs primarily following wake, following sleep, or during both behavioral states. Whatever

the roles sleep plays in learning and memory, it is clear that it is related in some fashion. What remains is to elucidate the complex interplay between waking and sleeping neurophysiology and how this interplay alters neural functioning in order to improve performance and consolidate a variety of distinct memory functions.

Recurrent sleep restriction and acute total sleep deprivation

Most studies of sleep loss use sleep deprivation paradigms, whereby sleep time is reduced to zero or near zero for an acute period of time. Individuals in these experiments generally undergo somewhere between 24-90 hours of continuous wakefulness. Though this paradigm does result in drastically impaired performance, altered mood, and altered brain function, it is harder to imagine how this could relate to real-world experience. That is to say, most individuals do not deprive themselves of sleep for this many hours contiguously, though it does happen in some industries (Buysse et al., 2003; Dawson & Zee, 2005). What is far more common is for individuals to curtail their sleep to between 4-6 hours per night (National Sleep Foundation, 2005). The obvious question is then, 'does recurrently restricted sleep result in similar impairments in mood, performance, and brain function?' And further, 'are there any differences in the response to recurrently restricted sleep and acute total sleep deprivation?'

Early studies of sleep restriction provide mixed results, with some studies showing impaired performance after restricted sleep (Webb & Agnew, 1965, 1974), and others showing no discernable performance impairments (Friedmann et al., 1977). Though Webb's later study showed impairments that persisted for 60 days, they found

impairments only on the Wilkinson Vigilance task. These impairments were mainly a reduction in correct responses, i.e. lapses, and were so minor that Webb concluded that "loss of sleep as much as 2 ½ hours a night is not likely to result in major behavioral consequences" (Webb & Agnew, 1974). The study by Friedmann and colleagues followed subjects for 6-8 months using a large battery of performance measures and discovered only minor lapsing effects (Friedmann et al., 1977). A systematic study of sleep restriction was conducted by Wilkinson evidencing that impairments did not become evident until sleep amounts were reduced below three hours (R.T. Wilkinson, 1969). These data, particularly Wilkinson's, led Horne to hypothesize that normal sleep contained a 'core sleep' consisting of the first 4-5 hours of sleep which is dominated by SWS, and the 'optional sleep' period which is dominated by REM and stage 2 sleep (J. Horne, 1988). The above studies, however, were generally small, and did not continuously monitor subjects. Indeed, it would be impractical to monitor subjects continuously in several month long studies. The consequence of this is that napping throughout the day and caffeine consumption may have occurred. More recent constant routine laboratory studies, using more sensitive performance measures with more thorough subject monitoring procedures, have recorded performance deficits on a variety of tasks occurring with sleep régimes as long as 6 or 7 hours per night for one to two weeks (Belenky et al., 2003; Van Dongen et al., 2003).

The more recent studies that have examined this issue have shown that performance impairments do not become apparent until at least two days unless the reduction is greater than four hours (Belenky et al., 2003; D. F. Dinges et al., 1997;

Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Jewett, Dijk, Kronauer, & Dinges, 1999; Van Dongen et al., 2003). However, as sleep is recurrently restricted over a period of days or weeks, the performance impairments continue to worsen (Belenky et al., 2003; D. F. Dinges et al., 1997; Van Dongen et al., 2003). In terms of PVT lapses, restriction to four hours per night for a week is equivalent to going a night without sleep, and two weeks of like restriction is roughly equivalent of spending two and a half to three days without sleep (Van Dongen et al., 2003). Interestingly, this effect is task-dependent. On the digit symbol substitution task, performance after two weeks of restricted sleep to four hours per night is no worse than after a night without sleep (Van Dongen et al., 2003). On the serial addition/subtraction task, performance was never as bad after two weeks of sleep restriction to 4 or 6 hours per night as following total sleep deprivation even for one night (Van Dongen et al., 2003). In addition to performance, recurrent sleep restriction results in altered mood (Blagrove et al., 1995; D. F. Dinges et al., 1997; Webb & Agnew, 1974). Thus, it appears that given enough restricted sleep, similar performance impairments and mood alterations become apparent, though the two are not equivalent. Though not equivalent, performance impairments resulting from recurrent sleep restriction and acute total sleep deprivation cover similar cognitive domains such as flexible thinking, attention, and working memory (Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Van Dongen et al., 2003). This manifests as performance alterations such as slower response times, increased number of lapses, increased response time variability, incorrect responding, and increased likelihood of making perseverative

errors (Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Van Dongen et al., 2003).

One very important difference between acute total sleep deprivation and recurrent sleep restriction is in the subjective measures of sleepiness. Totally sleep-deprived individuals will rate themselves as getting sleepier every day they are continuously awake (Froberg, 1977; Van Dongen et al., 2003). However, the rate of increase in subjective sleepiness in a recurrent sleep restriction paradigm is much less pronounced. After two weeks of sleep restricted to four hours per night, subjective ratings of sleepiness are no higher than after a night of sleep deprivation (Van Dongen et al., 2003). This is true, even though they are performing as if they had been awake continuously for 60-72 hours.

It remains to be seen whether or not extended or "chronic" sleep restriction results in even more impaired performance levels. This is an important question as many individuals curtail their sleep to four to six hours a night as part of their daily routine (National Sleep Foundation, 2005). In addition, many individuals have their sleep disrupted by sleep disorders (Weyerer & Dilling, 1991; Young et al., 1993). This is of particular importance in older adults, as the prevalence of sleep disorders increases with age, and age results in alterations in sleep architecture and duration even in healthy old adults (Foley et al., 1995; Monjan, 1990; Van Cauter et al., 2000). This converges with evidence suggesting that sleep loss has similar effects on performance and brain activation as that observed in normal aging (see 'aging and sleep deprivation' below, (Chee & Choo, 2004; Choo et al., 2005; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Habeck et al., 2004; Harrison et al., 2000). These studies, along with

others have caused some stress experts to view chronic or repeated sleep loss as an allostatic stressor which may cause long term changes in central and peripheral physiology (McEwen, 2006). Therefore, future studies should examine the effect of chronically reduced sleep to help determine the overall impact of sleep loss on these populations and, given the relationship between sleep loss and accidents, on society as a whole.

Inter and Intra Individual variability in the response to sleep deprivation

Though the effects of sleep deprivation and restriction are generally thought of as detrimental to performance, the degree to which performance is affected appears to vary between individuals and between tasks within individuals (Frey, Badia, & Wright, 2004; Leproult et al., 2003; Turner et al., 2007; Van Dongen, Baynard, Maislin, & Dinges, 2004; Van Dongen, Caldwell, & Caldwell, 2006; Webb & Levy, 1984; R. T. Wilkinson, 1961). The range of this variability can be quite large, with some individuals resisting performance impairments on the PVT for up to 72 to 88 hours, while others are impaired after less than 20 hours (Van Dongen et al., 2007). This differential response to sleep deprivation is quite stable within individuals across multiple testing sessions (Lim et al., 2007; Van Dongen et al., 2004; Van Dongen et al., 2006; Webb & Levy, 1984). This issue of individual variability was first examined by Webb and Wilkinson, though they were more concerned at the time with differences across repeated sleep deprivation sessions (Webb & Levy, 1984; R. T. Wilkinson, 1961). The theory was that either subjects would continue to worsen due to greater motivation and boredom effects, or

would improve as an adaptation to the stress of sleep loss (Webb & Levy, 1984). In these studies, subjects were repeatedly stressed with sleep deprivation on several occasions (five times in Webb's study and six times in Wilkinson's study). Wilkinson's early study showed that performance on a five choice reaction time task continued to deteriorate on subsequent sleep deprivation visits, and this was interpreted to be due to decreased motivation caused by boredom (R. T. Wilkinson, 1961). However, these six periods of deprivation were only spaced out by 1 week, and thus residual sleep deprivation may have been the cause for the continual decrease in performance across sessions. Wilkinson additionally noted that the degree to which performance was affected by sleep deprivation varied widely from individual to individual. Webb's follow-up study was small, having only six subjects (and no women), but it contained several strengths. This study spaced the five sleep deprivation sessions apart by three weeks, deprived subjects of two nights of sleep upon each visit, and tested subjects on a large battery of subjective ratings and neurobehavioral tests, including ratings of mood and tests of auditory vigilance, verbal working memory, visual search, logical reasoning, remote associations, and mental calculations (Webb & Levy, 1984). Though two tests showed significant changes across repeated sessions of sleep deprivation (logical reasoning and remote association), Webb noted that performance was similar within subjects across most tasks. He further noted that the response to sleep deprivation varied across subjects with some subjects being more sensitive to the effects of sleep deprivation than others. Thus, one never truly 'gets used to' the effects of sleep deprivation, and responses are not only similar within a person but vary widely across individuals.

The source of this variability across individuals is unknown, but at least one component appears to be trait-like and independent of recent sleep history (Van Dongen et al., 2004). This reliability appears to hold across multiple tasks, and can explain as much as 58% of the variance attributed to sleep deprivation (Frey et al., 2004; Van Dongen et al., 2004). But, an individual's response to sleep deprivation in one cognitive domain may not predict an individual's response to another (Frey et al., 2004; Leproult et al., 2003; Van Dongen et al., 2004). For example, the effects of sleep deprivation on subjective and objective measures of alertness are stable within individuals but also unrelated to each other (Leproult et al., 2003). Nocturnal increases in plasma glucose (an indirect measure of decreased glucose utilization by the brain) and relative increases in high alpha (10.5 to 12.5 Hz range) were highly correlated with each other and with subjective measures of alertness. These data suggest that a global reduction in brain activity relative to rested wakefulness may be related to subjective sleepiness. Other studies have confirmed that sleep deprivation reduces global glucose utilization by the brain (Thomas et al., 2000). In contrast, no measure, including change in delta power, correlated with objective performance changes in Leproult's study (Leproult et al., 2003). This suggests that objective alertness and subjective alertness are mediated by distinct, independent neural processes. The neural processes that mediate objective alertness remain to be elucidated.

In Leproult's study, the effects of sleep deprivation on lapses and reaction times were not only correlated from one session to the next, but worsened upon the second visit, which occurred two to six weeks later (Leproult et al., 2003). This worsening of

performance over repeated sessions is consistent with the studies of Webb and Wilkinson (Leproult et al., 2003; Webb & Levy, 1984; R. T. Wilkinson, 1961). A more recent study also reproduced this phenomenon on a working memory task with repeated sessions occurring from one month to a year apart from each other (Lim et al., 2007). This was not a global effect of session repeating, as the difference in performance accuracy from session one to session two was roughly 10% in the sleep-deprived condition and only 2-3% in the rested condition, highlighting an increase in the drop in performance accuracy in the second session (roughly 12% drop in session one and a 20% drop in session 2 (Lim et al., 2007). The cause of this worsening remains to be elucidated, be it an effect of reduced motivation due to boredom, residual sleepiness (which is unlikely to persist for six weeks to a year), or a build-up of allostatic load in response to repeated sleep deprivation (see above section 'Recurrent sleep restriction and acute total sleep deprivation'). This last possibility is particularly troubling, as it suggests the more one is sleep-deprived, the less one will be able to cope with it. If this turns out to be related to permanent structural changes in brain physiology (such as neuronal cell death), as McEwan suggests it may be, we as sleep researchers and as employers in government and industry must re-evaluate the ethical implications of continually restricting sleep in our subjects and working populations (McEwen, 2006). Evidence for this possibility of sleep-deprivation caused neuron death remains mixed and inconclusive (Biswas, Mishra, & Mallick, 2006; Cirelli, Shaw, Rechtschaffen, & Tononi, 1999).

Where other studies merely commented qualitatively (Webb & Levy, 1984; R. T. Wilkinson, 1961) or used correlational or factor analysis techniques (Frey et al., 2004;

Leproult et al., 2003), Van Dongen's studies utilized the intraclass correlation coefficient (ICC) approach to quantify the amount of variance explained by inter-individual variability (Van Dongen et al., 2004; Van Dongen et al., 2006). Using this method, Van Dongen determined that inter-individual variability in the response to sleep deprivation was distinct from baseline performance and prior sleep history, and this response varied between neurobehavioral tests (Van Dongen et al., 2004). Finally, Van Dongen observed that the intra-individual response to sleep deprivation, when examining the same task across multiple sessions, was highly consistent.

These data suggest that the effects of sleep deprivation are not global effects on the brain, but specific, localizable effects that may vary within individuals across multiple measures. The response to sleep deprivation within an individual varies across task type (Frey et al., 2004), and even across components within a cognitive task (Turner et al., 2007). Wright's examination of this issue of intra-individual variability is the largest study of individual differences to date, including 25 subjects (Frey et al., 2004). In this study, subjects underwent a battery of testing including tests of vigilance, divided attention, working memory, mental calculations, motor coordination, and objective alertness (Maintenance of Wakefulness Test). Strikingly, the top sleep-deprived performers on one task were among the bottom sleep-deprived performers on another. Hence, someone who is particularly vulnerable to sleep deprivation on one task may be particularly resilient on another. Since tasks generally target specific sets of cognitive abilities that rely on distinct neural networks, it is likely that individual differences in neural network properties drive the task-dependent aspect of the individual difference in

the response to sleep deprivation. However, equally striking was that at least one subject was a top sleep-deprived performer on multiple tasks (subject 110). Understanding the neurophysiologic correlates of such resilience in the face of sleep deprivation is crucial in order to derive ways to manage and minimize its effects across a variety of cognitive domains.

In response to this, studies began using functional imaging techniques to determine the source of variability within sleep-deprived states (Bell-McGinty et al., 2004; Chee & Choo, 2004; Chee et al., 2006; Chee & Chuah, 2007; Drummond et al., 2000) and whether this variability could be predicted by activation associated with performing the same and similar tasks when rested (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005). Additionally, functional activation changes associated with the individual variability in response to sleep deprivation are not only regionally specific, but reproducible across multiple sessions, particularly within the parietal lobes (Lim et al., 2007).

Functional imaging studies have been predominantly interested in explaining the individual variability in performance, rather than predicting them with baseline brain activation patterns, or reproducing brain activation patterns across multiple sessions. Drummond's early study of verbal learning associated better free recall after sleep deprivation with brain activation within bilateral parietal lobes, right temporal cortex, and left supplementary motor area (Drummond et al., 2000). It is not clear which neurobehavioral aspects of the task with which these activations are associated. It is also not clear whether these activation differences across subjects are related to each other.

Stern's group used a multivariate approach to identify networks of regions that decreased and increased as a function of sleep deprivation (Bell-McGinty et al., 2004). The degree of decreased activation after sleep deprivation (generally occipital, temporal, and posterior parietal regions) predicted recognition accuracy. Since these regions are not generally associated with working memory processes, this was interpreted to mean that individuals whom were more able to recruit attentional and visual processing resources when sleep-deprived performed more accurately. Chee's group was also able to show that left frontal and parietal recruitment in both rested and sleep deprived states were negatively correlated with performance decline (Chee et al., 2006). In contrast, additional studies by Chee's group was able to show that reduced deactivation within default mode areas such as posterior cingulate cortex (PCC) and medial prefrontal cortex, along with reduced deactivation of temporoparietal junction was associated with larger performance decline following sleep deprivation (Chee & Choo, 2004; Chee & Chuah, 2007). Thus, it appears that, at least within the sleep-deprived state, performance depends not only on increasing activation in a compensatory manner, but preservation of appropriate deactivation. This is similar in nature to the effects of aging on brain function (see below section titled 'Aging and sleep deprivation'), and highlights the importance of verifying whether activation increases are helpful or harmful to performance (Grady et al., 2006).

The first study to examine baseline brain activation differences in subjects who were previously identified as vulnerable or resilient to the effects of sleep deprivation found that only global activation levels were different after normal rest (Mu et al., 2005).

In every other way measured, including education years, baseline performance, age, and personality and sleepiness questionnaires these two groups of ten young men were identical. After sleep deprivation, the vulnerable group performed more poorly on their Sternberg working memory task, and activation differences became apparent. More specifically, both groups decreased activation globally with particular reductions within frontal and parietal regions. The vulnerable group lost more activity in left prefrontal and motor regions, whereas the resilient group maintained left prefrontal and motor activation. Interestingly, both groups lost parietal activation, but this did not affect their performance on this task. These data correspond with that from Chee's group, which showed that baseline left parietal and frontal activations were negatively correlated with performance change following sleep deprivation, suggesting these two regions may be particularly relevant when determining sleep deprivation susceptibility (Chee et al., 2006). It is important to note, however, that these studies both used working memory tasks. It may be that these activations are specific to the sleep deprivation resilience or vulnerability of a given individual's working memory processes. With regard to Mu's study, it is unclear what the global activation difference at baseline represents. Still, these studies highlight the importance and particular vulnerability of the prefrontal cortex to the stress of sleep loss.

A follow-up study by Caldwell re-examined this issue by associating working memory performance data during a 37 hour testing period with baseline activation associated with working memory collected 3 to 6 months after the sleep deprivation session (Caldwell et al., 2005). Thus, these data test the hypothesis that the association

between baseline activation and sleep-deprivation susceptibility is present even across a long period of time. As in their previous study, they determined that increased global activation levels were associated with decreased sleep deprivation susceptibility. However, no regional relationships were found, thus a clear understanding of the neurobiology of sleep deprivation susceptibility remains elusive.

Thus, there are three main findings regarding the association between brain activation and the effects of sleep deprivation on performance. Firstly, subjects who preserve parietal recruitment and increase or preserve left prefrontal recruitment when sleep-deprived tend to perform the best (Chee & Choo, 2004; Chee et al., 2006; Drummond et al., 2000; Mu et al., 2005). Secondly, subjects who show disinhibited default mode activation tend to perform more poorly (Chee & Choo, 2004; Chee et al., 2006; Drummond, Bischoff-Grethe et al., 2005; Lim et al., 2007). Thirdly, subjects who recruit more overall activation in the baseline rested state, particularly within the prefrontal and parietal regions, tend to perform better when sleep deprived (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005). It is important to note, however, that all of these studies generally examined brain activation associated with one task. As Wright's group pointed out, individual vulnerability depends on task type (Frey et al., 2004). Future studies need to examine the response to a multitude of tasks, particularly ones that target distinct parietal and prefrontal functions, over multiple sleep deprivation sessions while utilizing functional imaging methods. These types of studies may elucidate more clearly the role of the parietal and frontal lobes in inter and intra-individual variability in the response to sleep deprivation and other similar stressors. Further, it will be important

to elucidate the effects of sleep deprivation on brain function in combination with other commonly co-morbid stressors, such as chronic stress or aging. These types of studies will allow us to determine whether these individual differences are dependent upon common compensatory mechanisms and vulnerabilities, or whether the above effects are specific to sleep deprivation. Finally, given the recurrent finding that repeated sleep deprivation sessions result in increasingly poorer performance even when there has been ample time to recover, it becomes important to examine the long term effects of sleep loss (whether chronic partial or acute total) on brain physiology (Leproult et al., 2003; Lim et al., 2007; Webb & Levy, 1984; R. T. Wilkinson, 1961).

Aging and sleep deprivation

A constellation of studies suggest that aging and sleep deprivation (see above) impair a variety of cognitive functions, and alter task-related brain physiology. Striking is the similarity between these age and sleep deprivation effects (Chee & Choo, 2004; Choo et al., 2005; Grady et al., 2006; Habeck et al., 2004; Harrison et al., 2000; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). More specifically, similar to sleep deprivation, deficits in memory, inhibitory functioning, and attention are observed with advancing age (Backman et al., 1997; Cabeza, 2002; Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Cabeza, Grady et al., 1997; Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Cohen, 1988; Craik, 1983; Della-Maggiore et al., 2000; Glisky, Polster, & Routhieaux, 1995; Grady, 1998; Grady et al., 1998; Grady et al., 1995; Grady et al., 2006; Hasher & Zacks, 1988; Kausler & Hakami, 1982; Langenecker & Nielson, 2003; Mapstone, Rosler,

Hays, Gitelman, & Weintraub, 2001; McDowd & Filion, 1992; Nielson, Langenecker, & Garavan, 2002; Persson et al., 2007; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Salthouse, 1996; Schacter, Savage, Alpert, Rauch, & Albert, 1996; R. L. West, 1996). These performance deficits led to the generation of multiple theories attempting to explain them (Craik, 1983; Glisky et al., 1995; Hasher & Zacks, 1988; Salthouse, 1996; R. L. West, 1996). These theories range from a presumption of reduced attentional processing resources (Craik, 1983), reduced cognitive processing speed (Salthouse, 1996), diminished effectiveness of inhibitory processes (Hasher & Zacks, 1988), and selective frontal cortical sensitivity to aging (R. L. West, 1996). These theories are not incompatible, and it is possible that at least to some degree all of these factors contribute to the observed age-related decline in performance. Indeed, this last theory, regarding frontal cortical sensitivity, is particularly compatible as the frontal cortex is involved with all of these attention, inhibition, and memory functions (Luria, 1965; Mesulam, 1981, 1986; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). However, age-related decline in cognitive performance does not appear to be unitary across cognitive domains, i.e. the effects of age on cognitive performance differs by task within an individual as well as across individuals (similar to sleep deprivation) (Glisky et al., 1995). Indeed, West addresses the limitations of the frontal sensitivity hypothesis, suggesting that age-related deficits in item recall and recognition memory may be more associated with medial temporal lobe functioning (R. L. West, 1996). Thus, to fully understand the effects of age on performance, functional imaging techniques are necessary in order to link these performance changes with changes in neurophysiology.

Age-related performance deficits in episodic and working memory are among the most thoroughly studied with functional imaging techniques (Backman et al., 1997; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Grady et al., 1998; Grady et al., 1995; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000; Schacter et al., 1996). PET studies of episodic memory in young healthy individuals lead to the generation of the 'hemispheric encoding/retrieval asymmetry' (HERA) model, which describes that encoding generally relies on left prefrontal activity whereas retrieval relies on right prefrontal activity (Tulving et al., 1994). Aging generally impairs episodic memory performance, and alters this functional asymmetry (Backman et al., 1997; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Grady et al., 1995; Schacter et al., 1996). Instead of asymmetrically recruiting left and right prefrontal regions for encoding and retrieval processes respectively, older adults generally have reduced activity during encoding and recruit bilateral prefrontal regions during retrieval (Cabeza, Grady et al., 1997; Grady, 1998). These data, along with data from studies of spatial and verbal working memory (Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Reuter-Lorenz et al., 2000) and response inhibition (Nielson et al., 2002) led Cabeza towards the 'hemispheric asymmetry reduction in older adults' (HAROLD) model, which he argued generalized to a variety of cognitive domains including a variety of memory, inhibitory, and perceptual abilities (Cabeza, 2002). In short, the HAROLD model posits that when old individuals recruit neural networks to perform a given task, these networks are generally less lateralized than that observed in younger individuals. These alterations in brain activity

reflect not just simple regional changes, but changes in effective connectivity across networks of regions (Cabeza, McIntosh et al., 1997). Whether this change towards bilateral recruitment is due to recruitment of compensatory resources, reorganization of functional networks, disinhibition of unrelated or competing networks, a difference in cognitive strategies employed by the individual, or a combination of any of these factors remains unresolved.

These age-related alterations in task-dependent asymmetry of cortical activity are not the only age-related alterations in brain function. A careful examination of encoding, maintenance, and retrieval processes of working memory by Rypma and D'Esposito discerned age effects in dorsal but not ventral prefrontal regions (Rypma & D'Esposito, 2000). More specifically, working memory processes associated with the retrieval phase were localized to dorsal prefrontal regions, whereas encoding and retrieval processes were localized to ventral prefrontal regions. Greater activation in old adults was associated with faster working memory performance, whereas the opposite relationship was observed in young adults. However, there was a general reduction in overall activation in old adults in these dorsal regions. These data are supported by age-related structural changes in gray matter density, which appear to be largest within dorsal prefrontal regions (Raz et al., 1997; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Sowell et al., 2003). In order to explain these data, the authors suggested a sigmoid activation model, further stating that there was an age difference in the shape of this function. That is to say, low activation in old adults appeared to be close to no activation at all, whereas low activation in young adults was fairly high. In contrast, high activation

in old adults was similar to low activation in young adults, and high activation in young adults appeared at the asymptote of the sigmoid function.

More recently, newer data has suggested that age-related performance declines may also be due to changes in the so called 'default network'. This network is a series of regions that are more active in rest or control conditions than experimental conditions in a variety of tasks (Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001). These regions include medial prefrontal regions, ventral anterior cingulate and posterior cingulate regions, precuneus, and lateral parietal regions. This network of regions is hypothesized to be continuously active, relate to self-referential processing with particular attention to the internal milieu, and is generally subject to inhibition or suppressed activity during goal directed behaviors concerned less with the self and more with the external environment (Gusnard et al., 2001; Raichle et al., 2001). In addition, it has been proposed that this network of regions may contribute significantly to the generation of the concept of the "self". In particular, dorsal medial prefrontal regions may be associated with the "autobiographical" self (Gusnard et al., 2001). Others have gone further and suggested processing in these regions may reflect imagining events past and events that may occur in the future (Buckner & Vincent, 2007). Ultimately, these observations are speculative and based on post hoc assumptions. The meaning of this consistent, rest-related activity within medial frontal, cingulate and parietal regions remains unresolved and was recently a matter of debate (Buckner & Vincent, 2007; Morcom & Fletcher, 2007; Raichle & Snyder, 2007). The biggest critique of this default network is that it reflects activity associated with states of 'rest' which are nothing more

than states of unconstrained cognitive activity (Buckner & Vincent, 2007; Morcom & Fletcher, 2007). In spite of the critiques, it is clear that, similar to sleep deprivation, aging is associated with disinhibition of default mode regions during a variety of tasks (Grady et al., 2006; Persson et al., 2007). Further, this disinhibition is correlated with performance impairments across individuals (Persson et al., 2007). In the study by Persson and colleagues, high task demand resulted in greater decreases of default network activation (Persson et al., 2007). This was true in both young and old adults, but old adults had less deactivation overall, particularly during events of highest task demand. This was interpreted to be an age-related impairment of the ability to reduce interference effects and allocate and focus attention towards stimuli and processes that are immediately relevant (Persson et al., 2007). The implication of this is that a shift in the balance between default mode and task-related activity may make older individuals more susceptible to distraction (Grady et al., 2006). This in turn may impair a variety of cognitive functions.

Much like sleep deprivation, these age-related changes in default activity suggest that attentional impairments may be at the heart of age-related changes in cognition. Indeed, age is associated with alterations in attention (Chao & Knight, 1997; Filley & Cullum, 1994; Mani, Bedwell, & Miller, 2005; Mapstone et al., 2001; Parasuraman & Giambra, 1991; Parasuraman, Nestor, & Greenwood, 1989; Townsend, Adamo, & Haist, 2006), and it has been suggested that age-related deficits in a variety of cognitive domains can be attributed to attention deficits leading to inefficient processing rather than any categorical loss of function (Chao & Knight, 1997; Filley & Cullum, 1994; Isella et

al., 2008; Salthouse, 1996). Age-related deficits in sustained attention have been reported, and these deficits tend to be greater as time on task increases, as target stimuli become more degraded, and as event rate increases (Filley & Cullum, 1994; Isella et al., 2008; Parasuraman & Giambra, 1991; Parasuraman et al., 1989). These age-dependent vigilance decrements begin to appear in middle age adults (40-55 years of age), and continues to worsen into old age (70-80 years of age) (Parasuraman & Giambra, 1991). This effect is unaffected by twenty sessions practice, and is characterized by a stable increase in misses (lapses) and false alarms (errors of commission). The effect on misses is greater. Though these performance impairments seem canonical of sleep loss, Parasuraman suggested that this age difference was unlikely to be due to decreased arousal (Parasuraman & Giambra, 1991). He suggested that a higher event rate should increase arousal rather than decrease arousal. One could argue with this assertion, as performance decrements associated with sleep deprivation are magnified by higher presentation rates and cognitive demand (Heslegrave & Angus, 1985). Thus, it is possible to suggest that age-related decrements in sustained attention may be related to age-related decrements in general arousal level. This arousal decrement may interact with other age-related structural and functional changes in the nervous system to bring about the age-related performance changes observed across a variety of cognitive domains in addition to sustained attention.

Older adults also exhibit other attentional impairments, such as increased distractibility and reduced attentional focus (Chao & Knight, 1997; Mapstone et al., 2001). It has been suggested that impairments of sustained attention are at the heart of

these attentional impairments as well, due to reduced ability to suppress the effects of distracters over longer intervals (Chao & Knight, 1997). Performance on the continuous performance test (CPT), a canonical test of sustained attention, worsens with advancing age (Mani et al., 2005). Even when attention performance is similar in young and old adults, dramatic differences in the BOLD response is detected. An aging study of focal attention and attention shifting revealed that old adults recruited more frontal and parietal activity bilaterally than young adults to perform both tasks (Townsend et al., 2006). These data are consistent with Cabeza's HAROLD model (Cabeza, 2002). Hence, aging is associated with fundamental changes in multiple aspects of attention, and alters activity in frontal and parietal activation associated with attentional control (Chao & Knight, 1997; Townsend et al., 2006).

Unfortunately, the aging literature is plagued with many of the same interpretational issues that are common in studies of sleep deprivation when it comes to functional activation changes. Most frequently, functional imaging studies of aging are associated with age-related increases in activation when performance is preserved and decreases in activation when performance is impaired (Backman et al., 1997; Cabeza, 2002; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Grady et al., 1995; Langenecker & Nielson, 2003; Nielson et al., 2002; Reuter-Lorenz et al., 2000; Schacter et al., 1996; Townsend et al., 2006). Increased activation is generally thought of as compensatory in nature, particularly if performance is not different across age groups, whereas decreased activation is thought to reflect impaired processing efficiency (Backman et al., 1997;

Cabeza, 2002; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Langenecker & Nielson, 2003; Nielson et al., 2002; Persson et al., 2007; Reuter-Lorenz et al., 2000; Townsend et al., 2006). Alternative interpretations suggest these activation changes could be the result of disinhibition of task irrelevant regions (Cabeza, 2002; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Chao & Knight, 1997; Grady, 1998; Grady et al., 2006; Persson et al., 2007; Townsend et al., 2006). Thus increased activations could be harmful in certain circumstances. Additionally, decreased activation could simply reflect increased efficiency, particularly in the face of similar performance levels (Cabeza et al., 2000; Toh et al., 2001). Finally, recruitment of other, seemingly task irrelevant regions could reflect a reorganization of the functional anatomy associated with task performance, or the use of alternative, perhaps less optimal, behavioral strategies. Many of these interpretations are not mutually exclusive and may coexist in truth. Disentangling the possible interpretations from each other becomes crucial if the effects of aging on brain function are to be truly understood.

The most common method to address this is to correlate performance across subjects with activation across subjects (Cabeza, 2002; Cabeza, Grady et al., 1997; Grady, 1998; Grady et al., 1998; Grady et al., 2006; Langenecker & Nielson, 2003; Nielson et al., 2002; Persson et al., 2007; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000). However, if relationships in older or sleep-deprived subjects are merely less significant, this may be due to differences in signal to noise ratio due to increased variance in the BOLD response. Additionally, if relationships are more

significant in older adults, it may be the result of reduced variance across subjects in the younger group. Hence, within subject manipulations may have more power, specificity, and validity to detect changes in brain-behavior relationships, and should be used whenever possible.

Though performance-activation correlations may determine whether particular activations are helpful or harmful, this does not address whether these activation changes represent functional reorganization of a given cognitive approach, or utilization of alternate cognitive strategies (Backman et al., 1997; Cabeza, 2002; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Nielson et al., 2002; Reuter-Lorenz et al., 2000). Unfortunately, this is particularly difficult to ascertain, and the most commonly used tactic to address this issue is to carefully interview subjects post-experiment regarding any strategies that were employed during the experiment (Cabeza, 2002; Reuter-Lorenz et al., 2000). This issue is not easy to address, and it may continue to plague cognitive researchers for years to come.

In addition to these interpretational issues, evidence suggests that caution is advised when comparing fMRI data in young and old adults (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Huettel, Singerman, & McCarthy, 2001). The reason for this is that age may alter neurovascular coupling, thus changing the relationship between BOLD responses and the underlying neural activity (Buckner et al., 2000; D'Esposito et al., 1999; Huettel et al., 2001). Multiple studies examined several factors associated with the hemodynamic response

function (HRF) in order to address these concerns. The most consistent finding in all of these studies has been that BOLD responses are more variable in older adults, and this affects the spatial extent of activation (Buckner et al., 2000; D'Esposito et al., 1999; Huettel et al., 2001). Thus, when conducting analyses it is important to correct for unequal variances in the BOLD response, otherwise age differences may appear simply due to a reduction in the signal to noise ratio in older adults. This reduction in signal to noise may give rise to a larger spatial extent of activation in young adults, even in the absence of true neural activity differences. This would occur simply because larger noise would reduce the number of voxels that passed the statistical threshold (Buckner et al., 2000; D'Esposito et al., 1999; Huettel et al., 2001). The source of this increased variability is still unknown, though it is clear this is independent of age differences in head movements (D'Esposito et al., 1999; Huettel et al., 2001). In order to deal with this, Huettel and colleagues suggest increasing trial numbers, as signal to noise improves roughly as a function of the square root of the number of trials averaged together (Huettel et al., 2001). In addition to signal to noise ratio differences, Huettel and colleagues noted that hemodynamic response functions (HRFs) in older adults peaked and returned to baseline slightly earlier (Huettel et al., 2001). However, all other forms of the HRF appear to be similar, including peak amplitude, general shape, and refractory effects (Buckner et al., 2000; D'Esposito et al., 1999; Huettel et al., 2001). Because of these age-related differences, Buckner and colleagues cautioned interpretations of simple main effects in aging studies, but suggested that task by age interactions or parametric manipulations would provide valuable information regarding age-dependent changes in

brain activity (Buckner et al., 2000). D'Espisito and colleagues interpreted that the presence of age-related activity decreases *and* increases in the brain would likely reflect age-related changes in brain function. In contrast, decreased activity in the absence of any activity increases anywhere else in the brain would be more likely to reflect regional differences in hemodynamic coupling of neural activity (D'Esposito et al., 1999). Therefore, though the HRF appears to be minimally affected by age in terms of shape and temporal characteristics, increased variability in the BOLD response with increasing age makes interpreting simple main effects tricky. Age by task interactions may provide a clearer window into age-related changes in neural activation. Though untested, it is possible sleep deprivation causes similar problems. Studies of sleep deprivation and aging must, therefore, take into account the possibility that variances in the BOLD response are not equal across age and sleep states.

Though age and sleep deprivation can both alter brain activation and related performance, their interaction is poorly understood. The interacting effects of sleep loss and aging have only been examined in a few studies, and have met with mixed results (Adam, Retey, Khatami, & Landolt, 2006; Bonnet, 1989; Bonnet & Rosa, 1987; Philip et al., 2004; Webb, 1985; Webb & Levy, 1982). In a report by Webb and colleagues, old and young adults were subjected to sleep deprivation followed by a battery of tests targeting attention and cognitive function (Webb, 1985; Webb & Levy, 1982). In these studies, age-related differences appeared to be task dependent. In general, performance impairments following sleep deprivation were larger in older adults, particularly on tasks of attention. Where there were exceptions, younger subjects had higher baseline

performance which dropped after sleep deprivation to the level observed in older adults. However, it is important to note that the statistical analyses in these studies were fairly liberal and age-related differences in performance may have been erroneously inflated. Other studies suggest that old adults are actually *less* impaired by sleep loss, and this is evidenced by a smaller drop in performance (Adam et al., 2006; Bonnet, 1989; Bonnet & Rosa, 1987; Philip et al., 2004). However, as Webb pointed out, often times when performance drops are smaller in older adults, it is due to starting from a much lower baseline. In fact, this baseline is so low in the study by Philip and colleagues, that performance after sleep deprivation is not as bad as performance in rested older adults (Philip et al., 2004)! Though performance does not drop that much after sleep deprivation in this study, it appears to be a little worse. Thus, in absolute performance terms, older adults are not better at resisting sleep deprivation than younger adults. However, the study by Adam and colleagues showed that older adults have smaller drops and similar or mildly reduced baseline performance on various PVT measures (Adam et al., 2006). Thus, behavioral studies remain mixed, and this probably reflects task-dependent age effects (Webb, 1985; Webb & Levy, 1982). Further evidence to the fact that age differences are driven by baseline differences comes from a study by Harrison and Horne in which performance on tasks targeting prefrontal functioning in young, sleep-deprived adults is similar to that of rested old adults (Harrison et al., 2000). But, surprisingly, there is little evidence to suggest that the interaction of sleep loss and age worsens performance beyond that of age alone or sleep deprivation alone. This fact has

caused a lot of interpretational confusion as to how to conceptualize the effect of age on sleep deprivation performance effects.

Another possible interpretation is that residual effects of sleep loss may be present at baseline in old adults. Sleep quality and quantity measures are altered in old adults, whereby old adults have less deep SWS and REM sleep, less overall sleep time, and more wake after sleep onset (Van Cauter et al., 2000). From these data, and the data from Harrison and Horne, it is possible to speculate that an old adult is also a chronically sleep restricted adult (Harrison et al., 2000). Because of this, interpretations of age effects on sleep deprivation effects may fall victim to the nonlinearity of sleep loss effects on performance. Stated more simply, if one adult was sleep deprived for one night and another was not, and then you compared the effects of one night of sleep deprivation on both of these adults, you would have one adult with two nights of deprivation and another one night. If you looked at absolute performance, the adult with two nights would be worse, and would have a much worse baseline. If you looked at relative performance change, as Van Dongen's data suggests, the difference would be smaller between one night and two nights of deprivation than rested and one night of deprivation (Van Dongen et al., 2003). But one would never interpret that a night of sleep deprivation would make you resistant to the effects of additional sleep deprivation. In fact, one would make the opposite claim. Since performance does not obviously get that much worse in an old adult after sleep deprivation, it is unlikely that this interpretation of residual chronic sleep loss effects accounts for all of the age differences in the response to sleep loss. However,

that does not rule out the possibility that residual chronic sleep loss plays a role in these age effects.

As the age and sleep loss-related prefrontal hypotheses suggest (see above), it may be that both age and sleep loss target prefrontal functioning. Once targeted, performance will decline as prefrontal influences on behavior will be reduced or removed. Thus, if both age and sleep deprivation have this effect; either one or their interaction will result in the same effect: an inability to recruit prefrontal regions effectively to sculpt behavioral responses to become contextually relevant behaviors. As suggested by Mesulam (Mesulam, 1986), prefrontal damage leads to impairments that are not overtly obvious, though still critical to performance. Thus, reduced prefrontal involvement may only be able to impair performance so much. In short, it may be that you either recruit the prefrontal cortex correctly or you don't, and age may already impair prefrontal functioning.

An analogy may make this easier to understand. If a person tears a tendon in the right leg, this may impair that person's ability to walk. If that person instead broke a bone, walking may also be out of the picture. However, if that very person tore a tendon *and* broke a bone, the outcome would be the same as either of the above alone. But it would be inaccurate, even silly, to assume that a person with a torn tendon is more resistant to the effects of a broken bone (or vice versa) simply because the walking impairment was increased by less. Indeed, that person would need to heal *both* of these impairments before walking again.

This analogy illustrates the complexity of the age by sleep deprivation interaction, and suggests that a way of examining the issue would be to see if adults unaffected by the effects of age are affected more, less, or the same by sleep deprivation. This could then answer the question of whether or not older adults were affected less, more, or similarly by sleep deprivation. If it is simply a matter of recruiting prefrontal regions which are impaired generically by a variety of stressors, then older adults resistant to the effects of age should be affected by sleep deprivation similarly as young adults. If older adults are less affected by sleep deprivation as a whole, then these same age-resistant old adults should still be resistant to the effects of sleep deprivation.

Additionally, it will be important to examine whether the underlying neurophysiology of individual variability in the response to sleep loss is altered by age. Some evidence for this fact comes from two separate studies of sleep deprivation. Taken together, these studies suggest that sleep deprivation alters metabolic activity within the frontal lobes differentially in the young and old (G. S. Smith et al., 1999; Wu et al., 2006). It is important to note, however, that at present no study has directly compared these responses across ages. Nevertheless, these data suggest that age and sleep deprivation will interact to affect neural responses within prefrontal cortex, though the specifics of that interaction are unclear. Therefore, to gain better understanding of prefrontal functioning and the effects of sleep loss and age on prefrontal functioning, studies must examine this interaction directly, comparing the effects of sleep loss on prefrontal functioning in young and old adults. These studies may then begin to shed

light on the effects of these stressors on performance and on the complexity of their interaction.

Physiology of mammalian sleep

In order to understand fully how the loss of sleep impairs behavior and alters related physiology, it becomes important to examine the physiology of sleep itself. Sleep is controlled by a complex neural system consisting of a large number of interacting nuclei which alter widespread brain activity and the way in which disparate brain systems interact (Braun et al., 1997; Kaufmann et al., 2006; Maquet, 2000; Maquet et al., 1997; Maquet et al., 1996; Massimini et al., 2005; Nofzinger et al., 2002; Nofzinger et al., 1997; Saper et al., 2001). The physiologic effects of sleep-wake state extend beyond the brain as sleep systems regulate a larger number of peripheral systems including those concerned with metabolic and immune function (Van Cauter, 1990). Though sleep is important for the regulation of physiological processes throughout the body, this review is primarily concerned with neurophysiology and the relevance of sleep to behavior (McEwen, 2006; Spiegel, Leproult, & Van Cauter, 1999; Spiegel, Sheridan, & Van Cauter, 2002; Van Cauter, 1990). Before getting into the specifics of the neural underpinnings of sleep regulatory mechanisms, it is important to understand exactly what sleep *is*.

Defining mammalian sleep: behavioral and physiological characteristics

It is my opinion that sleep must first be defined behaviorally, as there are a series of stereotypic behaviors (that make up what we know as 'sleep') that are common across a multitude of species despite large differences in physiology across these species (Campbell & Tobler, 1984; Siegel, 1995). One of the behavioral criteria is that sleep is a natural and reversible state of unconsciousness (W. C. Dement & Vaughan, 1999; Howell, 1913; Kleitman, 1963; Kryger, Roth, & Dement, 1994; Pieron, 1913). Kleitman argues this is a misleading term, and one should consider sleep as a state without 'wakefulness' rather than a state of without consciousness (Kleitman, 1963). This is particularly relevant when one considers rapid eye movement sleep, where one experiences some characteristics of consciousness in the form of dreams. Another way to describe this is that while one is asleep, there is a perceptual disengagement from the environment which results in a heightened threshold in responding to sensory stimuli (W. C. Dement & Vaughan, 1999; Kleitman, 1963; Kryger et al., 1994; Pieron, 1913). In addition, there is a depression of skeletal muscle activity, though it is important to note that this activity is not merely absent but at times actively suppressed, i.e. during REM sleep (Jouvet & Michel, 1959; Kleitman, 1963; Pieron, 1913). Another behavioral characteristic of sleep is that this behavior is associated with taking a species appropriate posture (Kleitman, 1963; Kryger et al., 1994). In mammals, this generally takes the form of recumbent posture and eye closure (Kryger et al., 1994). The final behavioral characteristic I will mention here is perhaps the most relevant to the current report. When sleep is deprived, it is generally met with the desire to sleep, and upon sleeping, there is

an exhibition of rebound (Kleitman, 1963; Kryger et al., 1994). By rebound, I mean that sleep appears to be more intense (interpreted so due to more extremely heightened sensory thresholds) and occurs for a longer duration.

Sleep has been examined in over 150 species (Campbell & Tobler, 1984). The aforementioned behavioral characteristics of sleep are generally conserved across a variety of these species including humans, mice, dogs, zebra finches, dolphins, zebrafish, aplysia, and even drosophila (Campbell & Tobler, 1984; Dave et al., 1998; Hendricks & Sehgal, 2004; Zhdanova, 2006). This species to species consistency argues for sleep's evolutionary importance. This is particularly true for underwater mammals, whom need to surface for air on a fairly regular basis. If sleep was of no evolutionary importance, then a much more parsimonious evolutionary trajectory would have been to do away with sleep altogether. Instead, dolphins, for example, predominately alternate which hemisphere 'sleeps' so that the dolphin can continue swimming and breathing (Campbell & Tobler, 1984). The evolutionary importance of sleep is further evidenced by evidence in dogs, rats, and drosophila, all of whom die when sufficiently deprived of sleep (Bentivoglio & Grassi-Zucconi, 1997; De Manaceine, 1894; Rechtschaffen, Gilliland, Bergmann, & Winter, 1983; Shaw, Tononi, Greenspan, & Robinson, 2002). Sleep is not exactly the same across species, however, as timing in the light/dark cycle, amount in a 24 hour period, and number of phases of sleep differs widely across species (Campbell & Tobler, 1984; Siegel, 1995). Mice and rats, for example, are usually nocturnally active and their sleep occurs during the day in numerous bouts of minutes in length (Campbell & Tobler, 1984). Humans, on the other hand, sleep generally in one or two phases each

for hours at a time (Campbell & Tobler, 1984). Despite these differences, all of these species sleep so long as you define sleep by the aforementioned behavioral characteristics rather than rigid mammal-based physiological criteria (which can be misleading) (Campbell & Tobler, 1984; Siegel, 1995).

Sleep is a pervasive and important behavior with a complex underlying physiology. For the sake of this report, I will be focusing primarily on the neurophysiology of human sleep. Many of the pioneering studies of sleep electroencephalography were conducted in the 1930s (Blake & Gerard, 1937; Loomis, Harvey, & Hobart, 1937). In a thorough study by Blake and Gerard, the predominance of distinct EEG waveforms was linked to the depth of sleep, i.e. arousability from sleep (Blake & Gerard, 1937). Later in the same year, Loomis and colleagues also reported distinct EEG waveforms associated with various "sleep states" (Loomis et al., 1937). The waveforms they described in their seminal studies are recognized today as sleep stage defining waveforms. Standard polysomnography (PSG) of human sleep includes measures of electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG) (Rechtschaffen & Kales, 1968). These provide measures of general brain activity summed over millions of neurons (EEG), muscle tone (EMG), and eye movements (EOG). PSG data demonstrates that sleep is not a unitary process, but is very heterogeneous across the night. In humans, there are two types of sleep, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Kryger et al., 1994; Rechtschaffen & Kales, 1968). NREM sleep can be broken down into a series of physiological stages, each with typical wave-forms. These stages are generally scored in

30 second epochs as either ‘wake’, ‘movement’, stage 1, stage 2, stage 3, stage 4, or REM sleep. Stage 1 occurs on the transition between sleep and wakefulness. EEG data in an awake individual is made up of high frequency and low amplitude waveforms in the gamma (20-40 hz), beta (12-19 hz), and alpha (8-12 hz) range (Kryger et al., 1994; Rechtschaffen & Kales, 1968). An individual who is relaxed and awake with eyes closed has a predominance of alpha waves which stem mostly from occipital regions (S. T. Lu, Kajola, Joutsiniemi, Knuutila, & Hari, 1992; Rechtschaffen & Kales, 1968). As one drifts into stage 1 sleep, eye movements become slow and rolling, alpha rhythms dampen and spread to more anterior regions and then give way to rhythms in the theta (4-8 hz) range (Kryger et al., 1994; S. T. Lu et al., 1992; Rechtschaffen & Kales, 1968). The presence of vertex waves (sharp brief high amplitude waves) can also occur. This period of sleep lasts only a few to several minutes at the onset of sleep, and is also called drowsy sleep or transitional sleep (Rechtschaffen & Kales, 1968). From this stage, individuals enter a stage predominated by slower frequency waveforms. In stage 2 sleep, k complexes (negative sharp waves followed immediately by a slower positive component lasting at least 0.5 s) and sleep spindles (low amplitude bursts of activity in the 12-14 hz range lasting at least 0.5 s) become present. Though sleep spindles can appear in other stages of sleep, they are most commonly associated with stage 2 sleep. Spindles are generated in the reticular nucleus of the thalamus, a nucleus that envelops the thalamus and alters functional interactions of neurons within cortico-thalamic loops (Scheibel & Scheibel, 1966; Steriade, Deschenes, Domich, & Mulle, 1985; Steriade, Domich, & Oakson, 1986; Steriade, Domich, Oakson, & Deschenes, 1987). Spindles are more likely

to occur on the upswing from a downward deflection, and can often be seen on the rising phase of a k complex or a slow wave (Rechtschaffen & Kales, 1968). As cortical neurons become increasingly synchronized, the occurrence of 'slow waves' becomes more prominent. These are high amplitude (at least 75μV), low frequency waveforms in the delta (0.5-4 hz) range (Kryger et al., 1994; Rechtschaffen & Kales, 1968). When slow waves are present in more than 20% of the epoch this is termed stage 3 sleep, and when they are present in more than 50% of the epoch this is termed stage 4 sleep (Kryger et al., 1994; Rechtschaffen & Kales, 1968). Most research studies combine measures of stage 3 and 4 sleep into a unitary measure termed 'slow wave sleep' as the predominant waveforms in these stages are delta waves or 'slow waves'. These waveforms appear to be generated in cortical regions, usually within the medial prefrontal region (most prominently at the site of Fz), though central and parietal regions can also give rise to slow waves (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004). These slow waves propagate throughout the cortex, 'traveling' at a rate of 1.2-7 m/s (Massimini et al., 2004). The function of such slow wave generation and propagation remains unclear, though many groups have hypothesized these slow waves are central to learning (see above section 'Sleep and memory systems: Learning, Consolidation, and Generalization'), dissipation of the homeostatic drive for sleep (Borbely, Baumann, Brandeis, Strauch, & Lehmann, 1981), regulation of energy expenditure (Tononi & Cirelli, 2003, 2006), or cellular restitution (Inoue, Honda, & Komoda, 1995). It is most likely involved in many if not all of these processes. Spindles have also been associated with learning (see above section 'Sleep and memory systems: Learning, Consolidation,

and Generalization'), and the fact that they are coupled to slow waves (Contreras & Steriade, 1995) may belie multistage neural interactions during sleep across wide-scale networks involving the cortex, hippocampus, and the thalamus (Buzsaki, 1996).

In contrast to NREM sleep, REM sleep (rapid eye movement sleep) is drastically different. Aspects of REM were first described by Loomis in 1937, though he did not realize it at the time. He instead confused it with stage 1 sleep, noting low amplitude voltage and eye movements (Loomis et al., 1937). It was first discovered in humans almost twenty years later (Aserinsky & Kleitman, 1953) and then soon after in cats (Jouvet & Michel, 1959). EEG rhythms during REM sleep look remarkably like those observed during stage 1 or wake. Theta rhythms predominate and alpha is more prominent than during stage 1, and rapid, 'jerking' eye movements are periodically observed (Aserinsky & Kleitman, 1953; Kleitman, 1963; Rechtschaffen & Kales, 1968). Additionally, muscle activity, as observed using EMG, is suppressed (Aserinsky & Kleitman, 1953; Kleitman, 1963; Rechtschaffen & Kales, 1968). Interestingly, this suppression occurs at the brainstem to spinal cord level, and not at the cortical level. That is to say, motor output commands are still being sent to the spinal cord to ultimately reach skeletal muscles. Yet, these commands are stopped by inhibitory interneurons in the ventral horn of the spinal cord, which receive inputs from the sublaterodorsal (SLD) nucleus of the periventricular gray and the medial parabrachial nucleus (MPB) and the intermediate ventromedial medulla (IVMM) (Fuller, Saper, & Lu, 2007; Kryger et al., 1994; J. Lu, Sherman, Devor, & Saper, 2006). These interneurons then inhibit lower order motor neurons from activating skeletal muscles (Fuller et al., 2007; Kryger et al.,

1994; J. Lu et al., 2006). Thus, this physiological state seems bizarre, even 'paradoxical'. These physiological observations, along with the observation that subjects could recall dreaming after woken from this state, led to the hypothesis that REM sleep was when active dreaming occurred (Aserinsky & Kleitman, 1953). Though it has been shown that dreams can occur in other stages of sleep, this provocative discovery led many to study the relationship between REM and dreaming.

As an individual falls asleep, that individual passes through these stages starting with stage one and progressing into the deeper stages of NREM sleep, ultimately reaching slow wave sleep SWS (Kryger et al., 1994; Rechtschaffen & Kales, 1968). Following this, that individual will then go into REM sleep. This cycle continues throughout the night, with each cycle taking roughly 60-120 minutes (Kryger et al., 1994; Rechtschaffen & Kales, 1968). The depth of sleep, measured as arousability from sleep, closely mimics this pattern (Blake & Gerard, 1937). This suggests that these waveforms are specifically correlated with the depth of sleep. A normal amount of sleep for humans is roughly 7-9 hours per night, and in this time period, an individual will cycle through these stages 4-5 times. As the night progresses, bouts of SWS become shorter and bouts of REM become longer. Along with this, delta waves show a gradual exponential decrease in amplitude, and REM density (expressed as number of eye movements per unit of time) increases (Kryger et al., 1994).

The above reports focus mostly on behavioral observations, subjective reports, and EEG measures of sleep architecture. Where EEG measures have in many ways become the gold standard for sleep measurement, they do have their limitations. One of

the most prominent limitations is the limitation of spatial resolution. EEG waveforms are measured from the scalp, and represent summations of activity in literally billions of neurons (Braun et al., 1997; Kryger et al., 1994). So, measures of electrical activity are measures of averaged signal over a large variety of interacting neural systems (see below '*neurobiological basis for mammalian sleep*'). This limits understanding of the underlying neurophysiology of sleep, providing as many questions as answers. For example, do sleep stages represent periods of specific brain activity, or simply dominance of specific brain activity? That is to say, are distinct neural systems that generate distinct sleep waveforms (e.g. k complexes, sleep spindles, delta waves, saw tooth waves) operating independently and in a dynamic manner rather than limited to their sleep stage? In other words, could REM-related processes occur in NREM sleep but be undetected due to the dominance of SWS processes in the EEG (Nielsen, 2000)? These questions cannot be answered with EEG, even high density EEG. One is limited to the perspectives of measuring overall brain states. Over the last few decades, new functional imaging techniques and heroic animal studies have provided insight into the neurophysiology of sleep (see below '*neurobiological basis for mammalian sleep*'). These new techniques will continue to pave the way toward a more sophisticated understanding of sleep neurophysiology.

Neurobiological basis for mammalian sleep

Among the earliest discoveries of sleep neurophysiology comes from studies of Hammond and Durham (Hammond, 1865). These series of physiologic studies in the

early to mid 19th century highlighted the profound neurovascular changes that occur with changes in sleep/wake states. Their observations were generated independently from each other through dog experiments and collections of observations in humans. What was noted was an obvious change in brain volume on the onset of sleep or anesthesia represented by a increasing of the distance from the skull to the brain surface. Additionally, the color of the brain changed, from a pink hue to a pale color with only 'black blood' flowing through it. Thus, it appeared that during sleep there was a global reduction in oxygenated blood flowing through the brain. Both of these investigators interpreted this to mean that sleep onset derives from an arresting of oxygenated blood flow to the brain, and wakefulness occurred when oxygenated blood flow was increased. Though this hypothesis is not commonly supported today, these observations yield an important point: global changes in blood oxygenation to the brain occur with changes in sleep/wake states. Though this change may not cause sleep it is associated with sleep and gives us an important insight into brain function during sleep. It also highlights the importance of examining fMRI studies of sleep carefully (this will be discussed briefly in the methods section).

In the early 20th century landmark studies of the physiology of sleep were conducted by Piéron and Ishimori (Bentivoglio & Grassi-Zucconi, 1997; Howell, 1913; Kleitman, 1963; Kubota, 1989; Pieron, 1913). Piéron and Ishimori independently searched for substances within the blood and brain that would induce sleep (Bentivoglio & Grassi-Zucconi, 1997; Howell, 1913; Kleitman, 1963; Kubota, 1989; Pieron, 1913). Both of these investigators succeeded in extracting substances from the brains of sleepy

dogs that when injected into other dogs induced sleepiness (Howell, 1913; Kubota, 1989; Pieron, 1913). Ishimori's work, receiving even less attention than Piéron's, was the first to demonstrate this effect, in 1909 (Kubota, 1989). He extracted a variety of substances from the brains of puppies using a variety of methods. The only substance that was more prominent in sleep-deprived puppies than rested puppies was extracted with hot alcohol. This substance was then injected subcutaneously into rested dogs. The effects of this injection were compared to those observed after injection of the same substance extracted from rested puppies. The results were rather profound. Injections extracted from sleep-deprived puppies resulted in clear sleepy behavior, whereas injections extracted from rested puppies initiated no such behavior. Below is a translation of some of Ishimori's observations (Kubota, 1989).

> "It became notably inactive, was reluctant to walk, remained in one place and showed little response when called. Even when given food, it showed no interest. When forced to walk, it had an uncertain gait and preferred to retreat to a corner of the room or beneath the desk. If left alone, it gradually closed its eyes, dropped its head and sat on the floor to sleep. In other words, the dog's overall attitude was undeniably one of extreme sleepiness."

Piéron's observations were similar, though methods were distinct (Howell, 1913; Kleitman, 1963; Kubota, 1989; Pieron, 1913). Both of these investigators concluded that the build-up of this substance was toxic, insoluble in alcohol, and soluble in water. These studies advanced the idea that a sleep promoting chemical agent was produced by the brain, and circulated throughout the body. The neural systems that control both the observed neurovascular changes and chemical production remained a mystery.

Following the First World War, a first glimpse at the answer to this mystery was obtained by the observations of Greek neurologist Baron Constantin von Economo (Dickman, 2001; von Economo, 1930; Wilkins & Brody, 1968). In his original report, he

noted that some patients were afflicted with “a kind of sleeping sickness” that started with headaches and tiredness and progressed to hypersomnia and delirium (Wilkins & Brody, 1968). The result of this sickness was often death, and those that recovered remained physically weakened for an extended period of time thereafter. Though this original report contained a handful of cases, in the years to come this sickness spread throughout North America and Europe. By the end of his career, von Economo had examined thousands of cases. In his original report, he named this sickness ‘encephalitis lethargica’, and after years of observation separated patients into three general categories: somnolent-ophthalmoplegic, hyperkinetic, and amyostatic-akinetic (Dickman, 2001; Wilkins & Brody, 1968). Of these three classifications, the first two are of interest for the current topic. The classification, somnolent-ophthalmoplegic, were the classic hypersomnic cases; and the second was a form of the encephalitis that resulted in the opposite effect. Namely, hyperkinetic patients were afflicted with a sort of chronic insomnia or “troubling sleeplessness” (Dickman, 2001). So here was a disease that resulted in damage to specific regions of the brain causing either profound sleepiness or profound sleeplessness. In a paper written towards the end of his career, he summarized these observations and described a new view of the neurobiology of sleep that is surprisingly similar to contemporary views (von Economo, 1930). Debunking many of the popular theories of his time, he went on to describe a neural system that incorporated brainstem, midbrain, and hypothalamic regions which initiates sleep/wake transitions. This region is then sensitive to a soporific factor circulating in the blood or in the cerebrospinal fluid (CSF). In this way, he united the data of Piéron with his observations

of patients with encephalitis lethargica, whom had lesions in distinct pontine brainstem, midbrain, and hypothalamic regions. This view informed and inspired Saper's so called 'sleep switch' which is widely regarded today as the neural system for the control of sleep and wake transitions (Saper et al., 2001).

Von Economo's view was supported by an elegant series of anatomical lesion studies (Kerkhofs & Lavie, 2000). In the early 1930s, a Belgian neurologist named Frédéric Bremer performed mesencephalic transaction experiments on cats (Kerkhofs & Lavie, 2000). His plan was not to study sleep, but the results on cerebral EEG were so profound he concluded, "the complete deafferentation (the olfactory and optic nerves excepted) of the brain in the cat, by a transection of the brainstem behind the third nerve which leaves in place the telencephalon, leads immediately to a functional state very similar, if not identical, to natural and barbiturate sleep" (Kerkhofs & Lavie, 2000). In a control experiment, transecting where the brain met the spinal cord, he noted the EEG being similar to awake control cats. These observations were further supported by the electrical stimulation studies of Moruzzi and Magoun (Moruzzi & Mangoun, 1949). Through a number of electrical stimulation studies, they described a set of 'ascending reticular relays' which activate the cortex. They termed this the 'reticular activating system', and suggested that it was these set of brainstem, midbrain, and hypothalamic nuclei that promote wakefulness. Their influence was proposed to reach the cortex through both their diffuse projections and through thalamic relays. This view is still held today, as contemporary experiments have continued to support these seminal observations.

The current model of sleep/wake regulation comes from a multitude of experimental data from Saper's group and others (Saper et al., 2001). In short, a number of wake promoting and sleep promoting centers reciprocally inhibit each other. Their interaction forms a bistable 'flip flop' switch that promotes stable sleep and wake periods (Saper et al., 2001). Wake promoting centers are localized to the brainstem, the midbrain, and the hypothalamus. Specifically, the noradrenergic locus coeruleus (LC), serotinergic raphé nucleus, histaminergic tuberomammillary nucleus (TMN) send their ascending projections through the basal forebrain and diffusely project throughout the cortex (Saper et al., 2001). The basal forebrain itself has been implicated in the control of sleep/wake states (Porkka-Heiskanen, Alanko, Kalinchuk, & Stenberg, 2002; Porkka-Heiskanen et al., 1997). In particular, it is here that some propose the so called "factor S" is generated (Porkka-Heiskanen et al., 2002; Porkka-Heiskanen et al., 1997). In the basal forebrain, specifically within cholinergic neurons of the substantia inominata and the magnocellular preoptic nucleus extracellular adenosine builds as hours of wakefulness continue (Arrigoni et al., 2006; Porkka-Heiskanen et al., 2002; Porkka-Heiskanen et al., 1997). This buildup is reduced as sleep is initiated in a manner similar to the dissipation of slow wave activity (SWA) (Porkka-Heiskanen et al., 2002; Porkka-Heiskanen et al., 1997). This extracellular adenosine acts to inhibit neuronal firing via acting on A_1 receptors (Arrigoni et al., 2006). These receptors where adenosine acts are the same receptors sensitive to the effects of caffeine, and thus many have suggested that the build-up of extracellular adenosine may be related to the build-up of the homeostatic drive for

sleep (Arrigoni et al., 2006; Porkka-Heiskanen et al., 2002; Porkka-Heiskanen et al., 1997; Snyder, Katims, Annau, Bruns, & Daly, 1981).

A second arm projects from the cholinergic laterodorsal tegmental nuclei (LDT) and pedunculopontine tegmental nuclei (PPT) to the thalamus, and then to the cortex (Saper et al., 2001). Both of these arms are stabilized and supported by orexigenic input from the lateral hypothalamic area (Saper et al., 2001). These orexin-containing neurons have been implicated in narcolepsy, a state of unstable sleep/wake patterns (Chemelli et al., 1999; Lin et al., 1999).

All of these nuclei work to promote wakefulness, and only two known sets of nuclei in the hypothalamus promotes the transition into sleep. The ventrolateral preoptic area (VLPO) is a small cluster of neurons containing GABA and galanin (inhibitory transmitters) that reciprocally inhibit all of these wakefulness-promoting centers (Saper et al., 2001). Additionally, more recently characterized neurons in the median preoptic nucleus (MnPN) also reciprocally inhibit all of these wakefulness-promoting centers and interact with the VLPO (Gvilia, Xu, McGinty, & Szymusiak, 2006). These neurons are thought to promote sleep/wake transitions while the VLPO stabilizes and maintains sleep/wake states (Gvilia et al., 2006). The interactions of these nuclei are even more complicated by the transition between NREM and REM sleep and wakefulness (Saper et al., 2001). During wakefulness, monoaminergic input from the LC, raphé and TMN is at its highest, as is orexigenic input from the lateral hypothalamic area. At this time, VLPO activity is at its lowest and cholinergic input from the LDT and PPT is present. In the transition to NREM sleep, activity in all these centers reduces except the VLPO which

increases. Neurons in the central cluster fire the most, and portions of the extended VLPO increase firing, but not as much. On the transition to REM sleep, monoaminergic input drops even further, and orexigenic input stays virtually silent. In contrast, cholinergic input is at its highest, even higher than during wakefulness. And the central portion of the VLPO reduces and the extended portion begins to fire more. These firing patterns continue throughout the night generating the EEG patterns observed in the PSG. I suspect the basal forebrain acts to coordinate sleep/wake transitions via inhibition of basal forebrain neurons and disinhibition of the VLPO.

An additional flip-flop switch has been proposed for the transition into and out of REM sleep (J. Lu et al., 2006). This switch involves 'REM on' neurons in the sublaterodorsal nucleus and 'REM off' neurons in the ventrolateral portion of the periaqueductal grey matter and in the lateral pontine tegmentum which reciprocally inhibit each other.

The effects of these relatively small clusters of neurons on cortical populations are quite profound. A number of functional imaging studies during REM and NREM sleep states have shown widespread differences in activity patterns in comparison to each other and wakefulness (Braun et al., 1997; Czisch et al., 2004; Kaufmann et al., 2006; Maquet et al., 1997; Maquet et al., 1996; Nofzinger et al., 2002; Nofzinger et al., 1997). NREM sleep and, in particular, SWS is associated with widespread cortical decreases in activity as observed by fMRI and PET studies (Braun et al., 1997; Czisch et al., 2004; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). These cortical decreases are throughout the dorsolateral prefrontal cortex, with slightly larger decreases in the right

hemisphere. Decreased activity in lateral parietal, cingulate, and parietotemporal junction areas are also observed (Braun et al., 1997; Czisch et al., 2004; Kaufmann et al., 2006; Nofzinger et al., 2002). Of interest is that all of these regions are heteromodal and transmodal association regions, which translate incoming sensory information into conscious experience and coordinate context-specific actions in response (Mesulam, 1998). Basic unimodal sensory cortex did not show suppressed activity in any of these studies, which is quite remarkable given the sensory threshold observed with deepening of sleep (Braun et al., 1997; Czisch et al., 2004; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). However, what was observed was a reduction in activity within brainstem, midbrain, thalamic, and hypothalamic structures, all of which coordinate the promotion of cortical arousal and deliver sensory information to the cortex (Braun et al., 1997; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). This suggests that the threshold for arousal by sensory input is mediated through the reticular nucleus of the thalamus and not by primary sensory cortex itself. Indeed, patients with primary insomnia show smaller decreases in metabolic rate within the ascending reticular activating system, including regions of brainstem, thalamus, hypothalamus, and cingulate cortex (Nofzinger et al., 2004). A consequence of this is reduced daytime metabolic activity within the ascending reticular activating system and profound reduced metabolic activity within the dorsolateral prefrontal cortex (Nofzinger et al., 2004). This is relevant, as it suggests that EEG measures may not be sensitive to the biological basis of insomnia, and that the experience of sleeplessness at night may be due to hyperactive arousal centers *during* sleep in addition to before sleep. And, in terms

of daytime dysfunction, brain activity in a patient with insomnia looks remarkably like that of a sleep-deprived individual. It is also important to note that regions that show the greatest sensitivity to sleep deprivation and insomnia are also those that decrease activity the most in the transition into NREM sleep. It is this convergence of data that leads me towards a view of sleep deprivation that I discuss below (see section entitled 'Unanswered questions').

Cortical activity patterns during REM sleep are distinct from that observed in SWS or NREM sleep in general. This was related by Hammond in 1865 in his review of the work of Dendy in the 1820s, though this observation received little notice. He described a dramatic increase in blood flow of the brain when a woman went from deep sleep to dreaming, though not as much as was observed in waking (Hammond, 1865). Recent PET and fMRI studies have supported this observation. In REM sleep, suppression of activity in lateral association cortex (such as dorsolateral prefrontal cortex) is maintained (to a lesser degree), but activation in limbic cortex, particularly regions of cingulate, amygdala, insula, orbitofrontal cortex, and pontine tegmentum is increased to similar levels observed in wakefulness or even above that observed during wakefulness (Braun et al., 1997; Maquet et al., 1996; Nofzinger et al., 1997). Thus, where NREM sleep appears to be associated primarily with suppressed activity within association cortex, REM sleep is associated with increased activity within limbic regions in the presence of suppressed activity within association cortex. The functionality of this is unclear, though this may be necessary the generation of dreams. Though dreams may occur in any sleep stage, it has been hypothesized that dreams dominate REM, and that

covert 'REM processes' may be responsible for NREM mentation as well (Nielsen, 2000). Since limbic and orbitofrontal regions are often associated with emotional and memory-related processing, it is possible that activity in these regions during REM sleep either generates dream content or ascribes such content with emotional significance.

Whatever the reason, these changes in neural activity across sleep states are widespread throughout the cortex. This suggests that though the neurobiology underlying the control of transitions into distinct sleep states may be relegated to the reticular activating system (or as Saper puts it, the 'ascending arousal system' (Saper et al., 2001)), sleep is a whole brain phenomenon. This is further supported by the fact that this ascending arousal system receives input from cortical regions as well, which presumably can alter sleep/wake behavior (Chou et al., 2002). Not only are gross changes in activity present, but it appears that the connectivity between brain regions change by sleep state. Specifically, Tononi's group used transmagnetic stimulation (TMS) to excite regions of the cortex in order to examine how this excitation affected activity elsewhere in the brain (Massimini et al., 2005). They noted that during wake this excitation affected distinct cortical regions, but that during SWS this excitation was limited to the area of stimulation. These data suggest that on the transition to SWS, connectivity between brain regions is suspended. This further suggests that slow waves, themselves, are by nature a local phenomenon, and thus reflect local cortical processing.

A short note on sleep and consciousness

Another point for which this report is not chiefly concerned with regards consciousness. For the purposes of this note, I will define consciousness as a sense of self-awareness, or a sense of "I" that is experiencing something (James, 1890; Monin, 1992). I would like to suggest that sleep is not merely a state of unconsciousness. In fact, I would argue, rather strongly that this is far from the case. It seems more reasonable to assert that NREM sleep represents a state of reversible unconsciousness, and that REM sleep represents a state of limited or altered consciousness (Hobson et al., 2000). With NREM sleep, one loses a sense of awareness. This is never more keenly observable than with the loss of a sense of time. Individuals who fall into NREM sleep will wake up with no concept of the amount of time that has passed in the interim. They are completely unaware of the preceding moments. The experience of REM sleep is another matter, particularly because dreams are so pervasive in REM sleep. The reason I make this claim is that dreams themselves offer a limited form of awareness, whereby an individual is able to follow the content of dreams and in some ways interact with them as an "I" experiencing them. When a dream report is given, it is described as something experienced, e.g. "I was on a mountain of cotton candy, and cats were raining down from the sky". These dreams are truly experienced. They are sensed and remembered as actions experienced and taken by an individual. Thus, I posit the difference between REM sleep and wakefulness is not of consciousness and unconsciousness but rather of the *nature* of consciousness. One is not unaware of the dream itself, but instead the nonsensical nature of it. These distinctions are reflective of the neurophysiology of these

sleep stages. Lateral association cortex is concerned with integrating the external world with internal knowledge in order to develop appropriate, context specific behaviors (Mesulam, 1998). This latter aspect, that of context specific processing is one for which the lateral prefrontal cortex is chiefly concerned (Mesulam, 1986). These regions, particularly lateral prefrontal cortex, are suppressed to a great extent throughout sleep, including REM sleep, the very regions critical for the context-specific evaluation of any scene or action. With these suppressed during REM sleep, one could imagine being 'unconscious' of the ridiculous nature of a given dream. But, this does not mean one is unconscious to the dream itself.

Hobson first described this idea of dreams as 'proto-consciousness' in his 'activation-input source-neuromodulation' model (AIM) (Hobson et al., 2000). Hobson's model is represented in three dimensional state space, i.e. one axis represents activation (low to high), one axis represents information flow (dominated by internal inputs to dominated by external inputs), and the third represents mode of information processing (high monoaminergic levels to high cholinergic levels). In waking, there are high monoaminergic levels, cortical desynchrony, and processing is driven dominantly by external inputs. In NREM sleep, monoaminergic and cholinergic levels are moderate, cortical activation is highly synchronized, and processing is driven dominantly by internal inputs. In REM sleep, cholinergic levels are high, cortical activation is desynchronized, and processing is driven by internal inputs. Throughout the night, the brain transitions between these distinct states of consciousness. It is Hobson's view that dreams themselves represent a distinct state of processing whereby the brain prepares

itself for conscious waking. In this way, large amounts of REM sleep in the fetus can prepare it for waking experiences even without experiencing waking. Whether the purpose of dreams is to prepare the brain for consciousness, or performs some other function which requires altered processing remains unclear. Nevertheless, what is clear is that consciousness changes distinctly from waking to NREM to REM. Thus, a logical assumption to make is that changes in the brain that correlate with these changes in sleep/wake states may be linked to conscious processing in some manner.

When one transitions into sleep, recent data shows that some of the first regions to be suppressed are the cingulate cortex, and medial frontal regions (Kaufmann et al., 2006). These regions have been hypothesized to be critical for self-referential behavior and the 'autobiographical self' (Gusnard et al., 2001). These regions are among those that are more active during REM sleep (Braun et al., 1997; Maquet et al., 1996; Nofzinger et al., 1997). Therefore, it is possible that conscious awareness depends on cingulate and medial prefrontal activity, but that the nature of consciousness depends on what neural systems are interacting with these regions. Tononi posits that it is not neural systems that are critical for consciousness, but rather the connectivity of those neural systems (Tononi & Koch, 2008). In addition to activity suppression in lateral association cortex that is characteristic of NREM sleep, he has shown that effective connectivity of these regions also breaks down (Massimini et al., 2005). Thus, processing is more local, and integration of information becomes virtually absent. As Mesulam has also posited, this integration is critical for conscious experience (Mesulam, 1998). The degree to which consciousness is suppressed and connectivity is reduced may be related to the

intensity of NREM sleep and the power of slow wave activity (SWA). If this is the case, it would explain why NREM parasomnias are often associated with confusional arousals, and why they are much more likely to occur in children as children have more intense SWA and much more SWS (Mason & Pack, 2007). As SWS and SWA decline with age, so do the occurrences of NREM parasomnias (perhaps to be replaced with microarousals) (Mason & Pack, 2007). I imagine most NREM parasomnias would represent a brain trying to act without consciousness directing it. Thus, actions are not remembered and are much more automated in character. These NREM parasomnias would occur, because the propagation of slow waves across the cortical mantel would require too much stimulus to stop or interrupt. Slow waves would inhibit local cortical desynchrony which may be required for distal network synchrony and connectivity. Thus, less inhibited regions and networks (such as primary motor regions) may act without the direction of the rest of the cortex. The result of this is an unconscious brain that acts, and perhaps that acting provides enough of a stimulus to awaken one totally into the confused state normally observed.

This lack of connectivity is no longer present during REM sleep by virtue of desynchronized EEG and more normal responses to TMS stimulation (Tononi & Koch, 2008). The view I postulate above (which is similar to that postulated by Hobson), and that of Tononi are not incompatible, as effective connectivity and activation can go hand in hand. In both cases, we argue for NREM sleep being a state of unconsciousness or reduced consciousness and REM sleep being a state of consciousness similar though not exactly the same as that experienced during wakefulness. It is therefore my suggestion

that future examinations of consciousness be they philosophical, psychological, or physiological in nature would benefit greatly from a closer examination of the neurophysiology of sleep.

Aging and sleep

Early studies of sleep in aging suggested that the sleep of older adults is more 'fragile' (Webb & Campbell, 1979). That is to say, older adults have less overall sleep time, sensory thresholds for arousal are lower, nighttime awakenings are more frequent, and when woken, older adults take longer to fall back asleep (Feinberg & Carlson, 1968; Kales et al., 1967; Van Cauter et al., 2000; Webb & Campbell, 1980). Older adults are also more sensitive to the 'first night effect', and thus may take longer to adapt to new or altered sleeping environments (Webb & Campbell, 1979). In terms of sleep staging, the most prominent effect is a reduction in slow wave sleep (particularly stage 4) and an increase in wake after sleep onset (WASO) (Feinberg & Carlson, 1968; Kales et al., 1967; Van Cauter et al., 2000). These changes occur as early as midlife and progress throughout the life span (Feinberg & Carlson, 1968; Van Cauter et al., 2000). REM sleep remains relatively preserved, though modest reductions are observed in late life (Van Cauter et al., 2000). However, the distributions of SWS and REM sleep are altered in the elderly, suggesting that REM may be more disrupted than is evidenced by total REM time. Specifically, SWS is less concentrated in the first half of the night and REM sleep is less concentrated in the second half of the night (Dijk, Beersma, & van den Hoofdakker, 1989; Kales et al., 1967). These age-related reductions in SWS are more

prominent in men than women, though women are more likely to report a sleep problem (Rediehs, Reis, & Creason, 1990). Feinberg related these changes in sleep to measures of brain metabolism, brain size, cortical cell density, and performance (Feinberg & Carlson, 1968). Many of these measures paralleled the changes in sleep. These data led him to the 'sleep-cognition hypothesis' which posits two relationships between sleep variables and brain function. The first of the relationships posited is between variables that change during childhood or adulthood, but remain relatively stable during maturity. The second concerns those variables that change during maturity. Feinberg suggested that NREM and REM variables and total sleep time are among the first set of variables, and SWS are in the second set of variables (Feinberg & Carlson, 1968). The first set of variables is suggested to be related to the capacity and availability of information storage, whereas the second were posited to relate to problem solving, creativity, and complex behavioral learning. Finally, Feinberg suggested that age-related changes in sleep variables, particularly total sleep time and WASO, were evidence for both decreased sleep need and efficiency to carry out sleep processes in older adults (Feinberg & Carlson, 1968). This interpretation highlights a debate in the literature that still exists today: whether old adults need less sleep or have a reduced capacity for sleep.

Dijk and colleagues utilized spectral analysis of EEG signals to address this question (Dijk et al., 1989). Reductions in spectral power in the delta and sigma frequencies were observed as early as midlife (Dijk et al., 1989). The effect on delta power is most prominent in the early part of the night (Dijk et al., 1989). In addition, beta frequency waves are also more commonly noted during REM in old adults, thus

making REM appear more like wakefulness (Kales et al., 1967). Thus, aging alters properties of slow waves, sleep spindles (i.e. sigma alterations), and characteristics of REM sleep (Dijk et al., 1989; Kales et al., 1967). In order to address the issue of sleep need versus capacity, Dijk and colleagues then examined the distribution of delta power across the night (Dijk et al., 1989). Delta power is generally highest at the beginning of sleep, during the first and most intense SWS period. Each successive period of SWS shows a spike in delta power that is lower than the previous spike. Applying a mathematical fit to these peaks throughout the night yields an exponential decay function; the slope of which can be represented as a decay rate in log units/hr. Dijk interpreted that the higher this decay rate, the more efficient sleep processes are at dissipating the homeostatic drive for sleep. Older adults showed not only reduced spectral power, but a significantly lower decay rate. His interpretation was that age-related changes in sleep cannot be explained simply by a reduction in sleep need, as homeostatic dissipation of the sleep drive (represented by decay rate in delta power) should have been similar if only sleep need changed (Dijk et al., 1989).

These age-related changes in sleep and the effects of sleep loss are of increasing importance. This is due to the fact that the proportion of the US population above the age of 65 is growing, from 4% in 1900 to 21% by 2050 (Monjan, 1990). In addition to the age-related changes in sleep, the prevalence of sleep disorders is higher in older adults (Foley et al., 1995; Monjan, 1990). These sleep disorders further impair sleep, health, and related performance (Foley et al., 1995; Monjan, 1990). Much of this increase in sleep disorders is explained by other health problems that impact sleep, though when this

is controlled for 8% of otherwise healthy elderly have insomnia problems and 27% have a chronic sleep complaint (Foley et al., 1995). Further, use of hypnotics in elderly populations has been associated with increased likelihood of sleep complaints rather than decreased likelihood (Almeida, Tamai, & Garrido, 1999; Foley et al., 1995). This has been interpreted to be due to feelings of sleepiness brought on by the use of the hypnotics, or side effects of hypnotics used for non-sleep health conditions (Almeida et al., 1999). However, it is also possible this is due to the fact that people with sleep problems are more likely to complain about them and seek treatment. If this is the case, this still suggests that in the elderly use of hypnotics is not optimal and sleep complaints are still prominent after hypnotic use (Almeida et al., 1999). Thus, age alters multiple physiological measures of sleep architecture, impairs sleep quality, and reduces sleep quantity. These age-related changes could be due to comorbid health conditions or caused by physiological changes associated directly with aging. The meaning and cause of these changes are still unclear. However, taking into account the level of sleep complaints in the elderly, an argument that speaks to reduced sleep need in the elderly appears weak.

Circadian biology and its interactions with sleep and wakefulness

The physiology of alertness, sleepiness, and sleep/wake behaviors in general are regulated by more than just a homeostatic drive for sleepiness. It is well known that performance impairments after 24 hours of continuous wakefulness are more severe than performance impairments after 36 hours of continuous wakefulness (Froberg, 1977).

This strange phenomenon suggests that sleep/wake behavior is regulated by more than one process. This secondary process is the circadian process. The word 'circadian' comes from Latin and translates to mean 'about a day' (Aschoff, 1965). It refers to the regulation of biological processes that occur in an organized fashion over a roughly 24 hour period. Circadian rhythms in one form or another exists in almost all species of life (Mittag, 1996), and exist because the Earth rotates on its axis every 24 hours (Turek, 1998; Turek, Dugovic, & Zee, 2001). Thus, every 24 hours, organisms face an environment that alternates between light and dark periods, and must align their behaviors to it to maximize survivability.

In order to cope with this ever changing environment, organisms evolved an internal clock, called the circadian clock (discussed below). The internal nature of this clock was first described by Jean Jacques d'Ortous de Mairan in 1729 in his study of plant leaf movements (Czeisler & Guilleminault, 1979). It was noted that plants kept in the dark still showed daily changes in leaf movements even in the absence of sunlight. Diurnal organization of behavior such as this is observable in all manner of species (Aschoff, 1965; Mittag, 1996; Turek et al., 2001). The clock that regulates this phenomenon controls a constellation of events within the body such as sleep/wake behavior, body temperature, hormone regulation, immune functions, metabolic functions, and many others around a roughly 24 hour rhythm (Aschoff, 1965; Czeisler et al., 1999; Dijk & Czeisler, 1995; Turek, 1998; Turek et al., 2001). Brain activity is also regulated by the circadian process, and thus it is not surprising that neurobehavioral performance is as well (Buysse et al., 2004; Froberg, 1977; Inouye & Kawamura, 1979; Kleitman, 1963;

Kryger et al., 1994; Toth, Kiss, Kosztolanyi, & Kondakor, 2007). Therefore, for the purposes of the current report, it becomes important to understand the effects of the circadian system on performance as the circadian clock interacts with the homeostatic drive for sleep to affect neurobehavioral performance.

The two process model of sleep regulation

Borbély's two process model of sleep regulation describes the influence of two distinct but interacting processes on NREM and REM sleep propensity across the diurnal cycle (Borbely, 1982). These two processes are process S, the homeostatic drive for sleep, and process C, the circadian process which oscillates about a 24 hour period. These processes interact to determine the depth and timing of sleep/wake states. Process S is described as a process that slowly builds up every hour an organism is awake. As process S builds, propensity for sleep, particularly NREM sleep increases. However, one does not get sleepier every hour an individual is awake. This is because, as process S increases throughout the day, process C is also on the rise, peaking in late afternoon to early evening. When process C begins to decline and process S continues to increase, sleep propensity increases. At the onset of sleep, periods of NREM sleep are characterized with the highest level of delta power, or slow wave activity. This diminishes in an exponential manner across the night. This is generally considered to reflect the dissipation of the homeostatic drive for sleep. In Borbély's model, NREM and REM sleep are mutually exclusive, representing distinct propensities. The duration and timing of NREM and REM sleep depends on the difference between the largely

homeostatic propensity for NREM sleep, and the largely circadian propensity for REM sleep. Thus, when sleep starts, NREM propensity is high, as process S is high, and NREM sleep dominates the first half of the night. But as the night progresses, process S is progressively reduced. Further, towards the end of the sleep period, the circadian rhythm of temperature reaches its nadir. It is at this time when REM propensity is at its highest. Therefore, as the night progresses, the inhibition of REM by NREM propensity is reduced, and REM periods dominate the second half of the sleep period. When the morning is over, process C begins to rise again, and REM propensity drops. Thus, naps in the middle of the day are generally dominated by NREM sleep. Borbély's model is based on a large body of experimental data, and is currently held as the model of sleep/wake regulation. This model has implications for daytime performance as it predicts circadian variations in performance, as well as predicting the effects of extended wakefulness or shortened sleep periods with great accuracy.

The Suprachiasmatic Nucleus of the Hypothalamus and its role in circadian regulation

In the first half of the 20th century, debate still raged over whether circadian rhythms were generated wholly by external factors or were emergent from interactions between an internal clock and environmental zeitgebers (Aschoff, 1965). It wasn't until the early 1970s that a possible neural substrate for endogenous rhythms was found. In 1972, Stephan and Zucker lesioned the suprachiasmatic nucleus (SCN) of the hypothalamus in 25 rats (Stephan & Zucker, 1972). The result was a loss of rhythmicity in their activity recordings. Seven years later, Inouye and Kawamura showed that the

circadian rhythmicity of neural activity throughout the brain was abolished if the SCN was isolated (Inouye & Kawamura, 1979). Yet, within this hypothalamic 'island', SCN neurons maintained a circadian rhythm of firing. Truly landmark studies followed a fortuitous discovery of a mutant hamster with a shortened circadian period (Ralph, Foster, Davis, & Menaker, 1990; Ralph & Menaker, 1988). When Menaker's group transplanted fetal SCN tissue in wild-type hamsters, the wild-type hamsters showed the circadian period of the donor animal (20 hours and 22 hours in homozygous and heterozygous animals respectively). When a mutant animal was transplanted with a wild-type SCN, the mutant showed normal wild-type rhythms (nearly 24 hours). These experiments truly demonstrated that an internal clock existed, and that that clock was located in the SCN of the hypothalamus.

A series of genetic studies in mice, drosophila, and neurospora led to the discovery of circadian genes whose regulation forms transcriptional-translational feedback loops that give rise to circadian oscillations (Dunlap, 1999; Ko & Takahashi, 2006; Turek et al., 2001). In the mammalian clock, core clock genes CLOCK and BMAL1 heterodimerize within the nucleus and initiate transcription of genes containing E-box elements (Gekakis et al., 1998; Ko & Takahashi, 2006). These genes consist of period, cryptochrome, rev-erb, and ROR. One feedback loop consists of period and cryptochrome which translocate to the cytoplasm, heterodimerize, and then become phosphorylated by casein kinase. This complex translocates back to the nucleus and then inhibits further transcription of BMAL1 and CLOCK. Another feedback look consists of ROR and rev-erb which promotes and inhibits BMAL1 expression, respectively. This

process takes roughly 24 hours to complete a cycle and thus forms the circadian period. This molecular clock extends beyond the core clock genes and regulates the transcription and action of a variety of genes responsible for a variety of functions throughout the body. Thus, perturbations of these core clock genes can result in a variety of physiological consequences including metabolic, fertility, sleep, and immune problems (Ko & Takahashi, 2006).

Recently, independent, rhythmic expressions of clock genes were demonstrated in almost every tissue of the body (Balsalobre, Damiola, & Schibler, 1998; Plautz, Kaneko, Hall, & Kay, 1997; Schibler & Sassone-Corsi, 2002). No longer was the SCN the generator of all rhythms in the body, but was rather the central pacemaker, entraining peripheral clocks throughout the body.

Circadian interactions with sleep and wakefulness

As mentioned above, sleep and circadian processes interact to organize the timing of sleep/wake behavior. But circadian processes affect more than just the timing of sleep. Mutations in clock genes can affect sleep and may cause circadian rhythm sleep disorders (Ebisawa et al., 2001; Naylor et al., 2000; K. J. Reid et al., 2001; Wisor et al., 2002). Mice with *clock* mutations sleep 1-2 hours less during a twenty four hour period and have less rebound REM after partial deprivation (Naylor et al., 2000). Mutations in *period*, specifically in per2 and per3, are associated with circadian rhythm sleep disorders of the advanced and delayed type (Ebisawa et al., 2001; K. J. Reid et al., 2001). Finally, *cryptochrome* knockout mice show an elevated NREM sleep drive (Wisor et al., 2002).

Thus, genetic mutations of mammalian clock genes can result in altered sleep patterns and altered characteristics of the homeostatic sleep drive.

In addition to this, the SCN promotes arousal level via projections to the hypothalamus and brainstem, and receives feedback from the VLPO (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Chou et al., 2002; Chou et al., 2003). More specifically, the SCN sends indirect projections to the locus coeruleus via the dorsomedial hypothalamus (Aston-Jones et al., 2001). Neural activity within the locus coeruleus shows a circadian rhythm in firing that is abolished with dorsomedial hypothalamic lesions (Aston-Jones et al., 2001). Dorsomedial hypothalamic neurons also project to the lateral hypothalamic area to promote activity within orexigenic neurons, and send an inhibitory projection to the VLPO (Chou et al., 2002; Chou et al., 2003). Feedback from the sleep system to the SCN has not been documented anatomically. However, studies have shown that vigilance state has a clear effect on the firing rate of neurons within the SCN, and selective deprivation of different sleep stages resulted in altered SCN firing (Deboer, Vansteensel, Detari, & Meijer, 2003). Specifically, SCN firing is lowest during NREM sleep, high during wake and REM sleep. This effect on SCN firing has not been tied to changes in circadian timing; however, it has been shown that sleep deprivation can cause phase shifts independent of activity (Antle & Mistlberger, 2000). Thus, though process S and process C are independent of each other they are also intertwined. This is as must be to successfully sculpt sleep/wake behavior into consolidated periods of sleep and wakefulness.

Behaviorally and physiologically, this means that circadian processes can affect sleep states and daytime performance (Campbell & Zulley, 1989; Carskadon & Dement, 1980; Froberg, 1977; Hull, Wright, & Czeisler, 2003; Kleitman, 1963; Lavie, 1987; Webb & Agnew, 1977). On a gross level, the circadian timing of sleep affects the quality and length of sleep (Czeisler, Weitzman, Moore-Ede, Zimmerman, & Knauer, 1980). Studies attempting to disentangle the effects of process S and process C generally use altered sleep/wake patterns in the form of shortened or lengthened 'days'. These can be as short as the 20 minute day, with 13 minutes awake and 7 minutes asleep, repeated throughout the experiment, or as long as a 36 hour day with 24 hours awake and 12 hours of attempted sleep (Carskadon & Dement, 1980; Lavie, 1987; Webb & Agnew, 1977). This allows monitoring of the propensity to sleep across the 24 hour circadian rhythm, as these periods are either too short or too long to entrain to. In terms of sleep states, NREM sleep, particularly SWS appears to be dominantly regulated homeostatically, i.e. the occurrence, magnitude, and duration of stages 3 and 4 sleep is determined by prior hours of wakefulness (Webb & Agnew, 1977). Time of day of sleep affects NREM characteristics, but the effect is relatively small (Campbell & Zulley, 1989; Carskadon & Dement, 1980; Webb & Agnew, 1977). REM sleep, on the other hand, is more driven by circadian influences. REM propensity follows the circadian process tightly, with its highest pressure coinciding with temperature minimum (Carskadon & Dement, 1980; Webb & Agnew, 1977). This effect of REM sleep propensity and duration is largely independent of the homeostatic drive, though the first occurrence of REM sleep is tied to the timing of sleep onset (Czeisler et al., 1980; Lavie, 1987; Webb & Agnew, 1977). Of

further interest is that at the times of peak sleep propensity, SWS and REM sleep are generally mutually exclusive. Carskadon reported that of 910 30 minute sleep episodes across a 5-6 day period, only 27 contained both SWS and REM sleep (Carskadon & Dement, 1980). This supports Saper's anatomical model of NREM-REM sleep switches that reciprocally inhibit each other to establish multiple, stable, and distinct sleep states (J. Lu et al., 2006; Saper et al., 2001). It is noteworthy that as the circadian process begins to ramp up, following its nadir (marked by temperature minimum) REM pressure is highest. What follows is pressure for wakefulness throughout the day. Both of these states show characteristics of cortical desynchrony as opposed to NREM sleep which has its pressure at its highest in the beginning of the sleep period, when the circadian process is at its low point and the homeostatic drive is at its highpoint. Thus, the circadian process impacts sleep characteristics, and this has broad implications for sleep/wake behavior and related neurophysiology.

It has been known for decades that time of day impacts performance level on a variety of measures (Froberg, 1977; Hull et al., 2003; Kleitman, 1963; Wright, Hull, & Czeisler, 2002). Kleitman examined a series of neurobehavioral and physical measures across the 24 hour cycle. In all of them, he noted that performance varied across the day being worse in the early morning and late evening and best in the late afternoon (Kleitman, 1963). He noted that this rhythm was almost identical to the inverse of the temperature rhythm (Kleitman, 1963). He went on to posit that body temperature itself may have a direct impact on performance (Kleitman, 1963). However, it is equally as likely that the circadian process itself controls both temperature and performance

rhythms. Czeisler's group demonstrated much later on that, in fact, both of these observations were true. The circadian process mediated temperature change and performance change across the day, but temperature changes independent of the circadian process were associated with performance change, too (Wright et al., 2002). They went on to show that though the circadian and homeostatic processes impacted subjective alertness, motivation, and thus performance; these alertness and motivation changes impact performance independently of the homeostatic and circadian processes (Hull et al., 2003). Froberg noted that this daily cycle in performance continued over the course of 72 hours (Froberg, 1977). Thus, performance after 24 hours of continuous wakefulness is worse than that observed after 36 hours. This continues suggesting that sleep deprivation dependent-performance change follows a function with both linear (homeostatic) and nonlinear (circadian) components (Froberg, 1977). Thus, performance on day two is worse than that observed on day one, but afternoon performance is better than that day's morning performance.

The seminal observation that the SCN alters neuronal firing throughout the brain in a circadian manner suggests these performance changes are driven by circadian changes in widespread brain activity (Inouye & Kawamura, 1979). Recent reports in humans show a circadian rhythm in brain activity throughout the brain (Buysse et al., 2004; Toth et al., 2007). Buysse's PET study examined regional metabolic rate throughout the brain in morning versus evening scans. Though this method of analysis cannot determine whether the effects are due to number of continuous hours awake or from the effects of the circadian drive, clear time of day effects are present (Buysse et al.,

2004). Analyses were compared to subjective rating of alertness, which appeared higher in the morning than the evening. In the morning, activity was greater in visual processing regions of occipital cortex and attentional regions in temporo-parietal cortex. Another activation that was presented but not noted was a large activation in the right dorsolateral prefrontal cortex that spread to right dorsomedial prefrontal cortex (see figure 2, (Buysse et al., 2004)). This may support Posner's hypothesis that the right frontal cortex promotes arousal (Posner, 1994). Interestingly, there was no left prefrontal activation in the morning. In contrast, evening scans were associated with greater metabolic activity in medial sub cortical regions and anterior cingulate cortex. These sub cortical regions covered mid brain, brainstem, and posterior hypothalamus. These data were interpreted through the perspective of Borbely's two process model (Borbely, 1982). It was hypothesized that in the evening, wake promoting regions within the brainstem, midbrain, and hypothalamus ramp up activity to maintain alertness in the face of continuing homeostatic build-up. This would occur, because of input from the circadian system. A more recent study using high density EEG demonstrated that changes in EEG activity across the day depended on the spectral frequency of that EEG activity (Toth et al., 2007). In this study, high density EEG recordings were obtained at three times of day (8:00, 14:00, and 20:00). EEG activity was examined within delta, theta, alpha, and beta frequency domains. In concurrence with Buysse's data, theta activity in the cingulate gyrus and medial frontal cortex increased from 8:00 to 14:00. An increase in left dorsolateral prefrontal cortex activity was observed in the theta and beta domain. This effect was more prominent at 20:00. Other increases in alpha, theta, and beta domains

were observed in more medial posterior regions within parietal, occipital, and temporo-parietal regions at 14:00. A change in alpha distribution was observed at 20:00 with a general increase throughout the cortex in the beta domain (except within the right dorsolateral prefrontal cortex). Together, the data from these studies suggest that as the day progresses, activity within higher frequency bands increases in the left prefrontal cortex and activity in the right prefrontal cortex decreases (Buysse et al., 2004; Toth et al., 2007). Though it is unclear whether this is related to circadian regulation or homeostatic regulation, these data suggest a relationship between dorsolateral prefrontal cortex activity and arousal level. In conclusion, studies of sleep loss, such as that presented in the current report must carefully design studies to account for circadian variation in performance, alertness, and brain activity or conclusions may become confounded or erroneous.

Aging and circadian rhythms

It is well known that aging is accompanied by changes in circadian rhythms. In general, older people are more advanced than younger people (Czeisler et al., 1992). That is to say, older people get up earlier in the day, and go to bed earlier at night. A potential cause of this is a general shortening of the circadian period with age (Pittendrigh & Daan, 1974). As may be expected from this, the latency to REM sleep is shortened in older adults (Weitzman, Moline, Czeisler, & Zimmerman, 1982). Underlying this may be changes in the amplitude of the circadian process, as evidenced by reduced amplitude of the temperature rhythm in older adults (Czeisler et al., 1992; Weitzman et al., 1982).

It has been suggested that these age-related changes in the circadian pacemaker result in some of the observed sleep/wake disturbances, including changes in sleep time and efficiency and number and duration or arousals during sleep (Czeisler et al., 1992; Weitzman et al., 1982). An underlying cause for these age-related changes in circadian rhythms may be the reduction in SCN volume with age (Swaab, Fliers, & Partiman, 1985). This effect on SCN volume is even more pronounced in patients with probable Alzheimer's disease, a condition known to show symptoms of disrupted sleep/wake rhythms (McCurry & Ancoli-Israel, 2003; Swaab et al., 1985). However, it is important to note that the changes in SCN volume did not become apparent until very old age (80-100 years), and age-related changes in sleep/wake behavior and related neurophysiology occurs much earlier (Feinberg & Carlson, 1968; Swaab et al., 1985; Van Cauter et al., 2000). It is possible that more subtle changes in SCN physiology may be present in earlier years. It is also possible that circadian alterations play more of a causal role later in life, when changes in REM sleep become more apparent (Van Cauter et al., 2000; Weitzman et al., 1982).

These effects are not limited to the nighttime, as daytime alertness peaks earlier in the circadian cycle in old adults (Czeisler et al., 1992). Corresponding changes in the relationship between circadian rhythms and daytime performance and mood are also observed (Monk, Buysse, Reynolds, Jarrett, & Kupfer, 1992). Specifically, young adults show clear circadian rhythms in alertness and performance even when wakefulness is extended beyond 16 hours to 36 hours or more (Froberg, 1977). For this reason, performance after 36 hours awake is less impaired than after 24 hours, when an

individual is at their circadian trough. This may not be true for old adults. Measures of vigor, affect, dexterity, visual search, verbal reasoning, and vigilance in old adults showed only linear impairments over a 36 hour period (Monk et al., 1992). That is to say, in old adults, there was no improvement in performance and mood due to the ramping up of the circadian process in the early morning. Thus, old adults appeared to be less affected by extended wakefulness during the night, as the ramping down of the circadian process did not affect them as severely. But, old adults also appeared more affected during the next day, as no circadian process rescued their performance and mood. Monk characterized these age-related changes in the interaction between circadian rhythms and sleep homeostasis rather elegantly (Monk et al., 1992):

> "With advancing age, the magnitude of the difference between night and day can become diminished, with wakefulness intruding into the night and sleep intruding into the day".

Hence, part of maintaining alert performance during the day requires maintaining restful sleep at night. This requires both a healthy circadian and homeostatic sleep system. A breakdown of both circadian and homeostatic processes is observed with aging; resulting in daytime consequences with respect to mood and performance. These consequences can be severe, mimicking that of a night without sleep (Harrison et al., 2000). Therefore, when examining the effects of the changes in one process experimentally, it is crucial to be mindful of the effects your experimental paradigm may have on the other process. This may be particularly important in aging research.

Recovering from sleep loss

For over a hundred years, almost countless studies have explored the detrimental effects of sleep loss on cognitive functioning. Yet, comparatively few studies have explored the process of recovery from sleep deprivation. This is in spite of the fact that part of the behavioral definition of sleep is that sleep deprivation is followed by a rebound of sleep that is more intense (Blake & Gerard, 1937; Carskadon & Dement, 1994; Durmer & Dinges, 2005; Kleitman, 1963). Characteristics of this increased intensity are reduced responsiveness to the environment in comparison to normal sleep, altered electroencephalographic properties of sleep (such as higher spectral power in the delta frequency), and increased sleep time and efficiency (Blake & Gerard, 1937; Borbely et al., 1981; Carskadon & Dement, 1994; Johnson, Slye, & Dement, 1965; Kleitman, 1963). However, the number of hours of sleep recovered is never as much as was lost (Gulevich, Dement, & Johnson, 1966; Johnson et al., 1965; Kales et al., 1970; Spiegel et al., 1999; Webb & Agnew, 1965). Nevertheless, in terms of performance, the effects of sleep loss appear to be entirely reversible, even if the amount of sleep loss is severe (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970; Spiegel et al., 1999; Webb & Agnew, 1965). The exact timeline for performance recovery, the relationship between recovery sleep physiology and performance, and the neural correlates of these variables remain largely unknown. Examining these variables is of critical importance, as they can shed some light on the processes that recover performance and potentially maintain performance after sleep loss.

The effect of sleep deprivation and recurrent sleep restriction on sleep physiology

Sleep after sleep loss is deeper than normal sleep. It can be profoundly so, if the sleep loss is great enough. One of the original reports of this observation comes from the seminal study of Patrick and Gilbert (Patrick & Gilbert, 1896). In this study, they used a pain stimulus to awaken the subject every hour throughout the sleep period. Remarkably, the sleep following 90 hours of continuous wakefulness was so deep that the experimenters had to apply electrical current directly; removing the pendulum and the resistance tube which varied and limited the current applied. In their report, they explained the degree of this increased sleep depth (Patrick & Gilbert, 1896):

> "The deepest sleep was found at the end of the second hour, when the subject could not be aroused sufficiently to ring the bell, but responded with a cry of pain. The next deepest sleep was found at the end of the first hour and the next at the third hour. The current used at these three times was altogether out of the question for the subject to endure when awake".

Over the next several decades, this observation of increased sleep depth following sleep loss was reconfirmed in many studies (Blake & Gerard, 1937; Kleitman, 1963; Pieron, 1913). Blake and Gerard showed that this effect was tied closely to the presence of slow waves in the EEG (Blake & Gerard, 1937). Indeed, the data suggest that, at least with acute total sleep deprivation, the most common effect is an increase in slow wave activity and time spent in slow wave sleep (Kales et al., 1970). However, if REM sleep is selectively deprived, REM sleep propensity increases (W. Dement, 1960). If sleep is chronically restricted or totally deprived for over 200 hours, recovery characteristics are less clear (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970; Spiegel et al., 1999; Webb & Agnew, 1965). Most of these studies suggest that both REM sleep and SWS rebound (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970; Spiegel et

al., 1999; Webb & Agnew, 1965). The time course of this recovery appears to depend on sleep stage. If SWS is deprived, or if sleep is totally deprived, then SWS propensity increases sharply over a one to two day period (H. W. Agnew, Jr., Webb, & Williams, 1964; Blake & Gerard, 1937; Borbely et al., 1981; Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970). Following this, sleep appears normal. However, in REM deprivation experiments, or experiments of chronic partial sleep loss, this response is not as apparent (W. Dement, 1960; Spiegel et al., 1999; Webb & Agnew, 1965). REM rebound may or may not be obvious on the first night, but usually becomes more obvious on subsequent nights, and this effect can persist for many days (W. Dement, 1960; Spiegel et al., 1999; Webb & Agnew, 1965). In studies of prolonged total sleep deprivation, i.e. 200 hours or more, both of these effects occur, with SWS rebounding more strongly on the first night, and REM on the subsequent nights. This observation led many to think that SWS was 'more important' than REM sleep (Kales et al., 1970; Webb & Agnew, 1965). However, if one applies Borbély's two process model to these data, an alternative explanation becomes apparent (Borbely, 1982). Normally, SWS propensity is high in the beginning of the night and low at the end of the night, when the circadian rhythm has reached its nadir. REM propensity shows the opposite relationship, with REM propensity peaking at the circadian nadir. However, if an individual is sleep deprived, the SWS propensity increases overall. Thus, this delayed REM rebound effect may be due to the fact that following sleep deprivation the difference between SWS propensity and REM propensity remains high even at the point when REM propensity is highest. Thus, REM rebound would be inhibited by the large drive for SWS. Further

evidence for this comes from the sleep onset times for many of these deprivation experiments. The timing of recovery sleep is generally in the early morning, when circadian pressure for REM sleep is at its highest (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970). However, since SWS pressure is also high, REM onset may be inhibited until the second or third recovery day. This effect may explain why SWS recovery appears to occur more acutely and rapidly, whereas REM recovery may take days. Thus, time of day of sleep can determine the characteristics of recovery sleep. In order to control for these effects, placing recovery sleep at the same time of day as baseline sleep is necessary. Even then, the increased homeostatic drive for sleep may inhibit REM rebound until the second night.

The increase in the amount of REM and SWS following sleep deprivation is not the only change observed. In almost all of these studies, recovery sleep was generally associated with a reduction in the percentage of stage 2 sleep (H. W. Agnew, Jr. et al., 1964; Borbely et al., 1981; Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970). However, it is important to note that sleep spindles, which primarily occur during stage 2 sleep, increase in frequency, and are more likely to occur during REM sleep on recovery nights (Kales et al., 1970). This suggests that though stage 2 sleep time decreases, characteristic waveforms of stage 2 are more prominent. In addition, slow wave amplitude increases and REM density, represented as density of eye movements, increases (Borbely et al., 1981; Kales et al., 1970). Thus, not only does a sleep-deprived individual spend more time in SWS and REM, but the intensity of all sleep stages increases. This is supported by the observation of increased arousal threshold throughout

sleep, and decreased wake and movement time (Blake & Gerard, 1937; Kleitman, 1963; Patrick & Gilbert, 1896; Pieron, 1913).

Recovery sleep in old adults also shows these characteristic changes, however, they are not as robust as in young adults (Bonnet, 1989; Bonnet & Arand, 1989; Carskadon & Dement, 1985; Reynolds et al., 1986; Webb, 1981). Specifically, old adults show increased SWS following sleep deprivation, but this increase is not as large as that observed in young adults (Bonnet, 1989; Bonnet & Arand, 1989; Webb, 1981). This effect is magnified in men, with women having SWS increases more similar to that observed in young adults (Reynolds et al., 1986). REM rebound is detected on the first night with mild sleep deprivation regimes, unlike in young adults (Bonnet & Arand, 1989; Reynolds et al., 1986). Old adults also show decreased REM latency, with what appears to be an increased likelihood of sleep onset REMs (Bonnet & Arand, 1989; Reynolds et al., 1986). It has been posited that the reduced SWS in old adults allows for greater REM rebound in old adults (Bonnet & Arand, 1989). Thus, recovery sleep in old adults shows a similar yet smaller increase in depth and intensity. These results once again highlight the debate over whether old adults need less sleep or are able to get less sleep. If the former is true, then old adults should recover from sleep loss more quickly, if the latter, older adults should show performance impairments that persist for a longer period of time.

Recovering performance after sleep deprivation and sleep restriction

Even following extremely long periods of total sleep deprivation, cognitive performance is generally minimally impaired after one or two nights of sleep to recover (Bonnet, 1985; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Patrick & Gilbert, 1896; Rosa, Bonnet, & Warm, 1983; Williams et al., 1966; Williams et al., 1959). It is entirely unknown how this cognitive recovery is achieved. This is partly due to the fact that the specifics of performance recovery are poorly characterized and seem to depend on the duration of sleep recovery bouts and the task performed (Belenky et al., 2003; Bonnet, 1985, 1989; Bonnet & Arand, 1989; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Patrick & Gilbert, 1896; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). When given one night with 8-9 hours time in bed, studies generally show that impairments can persist for anywhere between one and three days (Belenky et al., 2003; Herscovitch & Broughton, 1981; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). This appears to be true for older adults as well (Bonnet, 1985). A night of ten or more hours in bed appears to result in mostly recovered performance in a single night, though some subtle differences may still remain (Gosselin et al., 2005; Herscovitch et al., 1980; Patrick & Gilbert, 1896).

As may be expected, residual performance impairments after recovery tend to be the same types of performance impairments that are the most severe after sleep deprivation, e.g. reaction time slowing, cognitive slowing, and increased false alarm rate (Bonnet, 1985; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al.,

1980; Patrick & Gilbert, 1896; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). These are impairments of attention and executive functioning, which rely on frontal-parietal networks (Cabeza & Nyberg, 2000; Mesulam, 1986). It has been posited that the prefrontal cortex is particularly sensitive to sleep loss (Harrison et al., 2000; Thomas et al., 2000). It then becomes likely that the prefrontal cortex may also take the longest to recover, enabling residual performance impairment for days following recovery from sleep deprivation. Indeed, a recent report has shown that metabolic activity within the prefrontal cortex has not yet returned to baseline levels after one night to recover (Wu et al., 2006). Age can also impair prefrontal function in a similar manner and sleep loss is common in aging (see above sections '*Aging and sleep deprivation*' and '*aging and sleep*'). It is then possible that age would affect the ability to recover from sleep loss. The few reports that have examined performance recovery following sleep loss in young and old adults show mixed results (Bonnet & Arand, 1989). However, a comparison of the data from Wu and colleagues and Smith and colleagues suggest that brain function following recovery from sleep deprivation is altered by age (G. S. Smith et al., 1999; Wu et al., 2006). Thus, it becomes important to determine whether or not age interacts to alter the recovery process, particularly with regards to prefrontal functioning.

Unanswered questions

The scientific understanding of sleep has advanced greatly over the last two hundred years. In the last fifty years alone, great leaps and bounds have been made on genetic, molecular, systems, and cognitive levels. We now know that sleep is not a

unitary process, but a complex, active, whole brain process. We know that a complex interplay of neurochemical systems control the balance between sleep and wake states. We know these neurochemical systems are complex and made up of brainstem, midbrain, thalamic, and hypothalamic nuclei which alter whole brain function on a gross level. We know that the loss of sleep has an impact on physiological systems throughout the body. We know that the loss of sleep impairs a wide variety of cognitive skills that rely on fronto-parietal functioning. We know that the best medicine for recovering from these impairments is to sleep. We know that this recovery sleep is more intense than regular sleep, and that this intensity is linked to spectral properties of the EEG. We know additionally that sleep actively promotes neuroplastic changes that are critical to learning processes. We know that aging is associated with changes in sleep and an increased risk for the development of sleep disorders that would further exacerbate these sleep changes. We know that behavioral impairments observed in aging are similar to behavioral impairments observed with sleep loss, and that the added stress of sleep loss to age results in a differential response. This knowledge, along with much more knowledge gained over the last two hundred years has allowed us to come to a better understanding of sleep, and to take this understanding and apply it at the level of the clinic and public policy.

However, there are still a lot of unanswered questions, which we are now finally on the verge of reaching. This disseration will attempt to address a small portion of these questions, particularly with regard to the effects of sleep loss and recovery on brain function. Recent data concerning sleep deprivation has used functional imaging techniques to examine the effects on brain function. This tool has shown us that the

whole brain is not affected equally by sleep deprivation. In fact, effects appear rather localized and task specific. That said, there also appear to be changes that are independent of task type. These are regions of the brain that are impacted by sleep deprivation across a wide variety of tasks. Thus, the effects of sleep loss on brain function are heterogeneous throughout the brain, with particularly large effects on fronto-parietal cortex. These data bring us to the question, 'what areas are affected by sleep loss the most, the least, and why?' Alongside this, these new data show us that the brain has the capacity to compensate for the effects of sleep loss. Some areas increase activation when sleep is deprived and these increases limit the occurrence of sleep loss dependent-errors. This leads us to the question, 'what areas can be recruited to compensate for sleep loss, and are these regions generic or specific to the task at hand?' Our knowledge of the link between the susceptibility of certain cognitive abilities and changes in specific neural networks that control those abilities remains limited. These questions in particular may be important for the advancement of an understanding of how to best manage sleep loss via targeted treatments such as drug treatments and technologies such as transcranial magnetic stimulation or direct current stimulation (Luber et al., 2008; Marshall et al., 2006; Marshall et al., 2004). The big questions these data ask are 1) 'why these specific changes in brain function', and 2) 'how are these changes relevant to the observed performance change?' Do these changes in brain function occur because of a change in cognitive strategy, a change in processing efficiency, or a functional reorganization of neural resources? That is to say, does a sleepy person solve the same problem in a different way, or does a sleepy person solve this problem in the same way but utilize the

brain differently to conduct the same processes? This, in particular, is important, because if we perform the task differently when sleepy, behavioral interventions may be able to mitigate the effects on performance. Fundamentally, we know that sleep loss can change brain function and impair performance, but we do not know why or how these two are linked. This is problematic as cognitive models of sleep loss are incomplete without full understanding of how sleep loss affects brain function. Moreover, we do not know what processes occur during recovery from sleep loss, and how these processes may recover performance. This, too, has implications for improved management of sleep loss via targeted treatments. If sleep is the best way to recover from sleep loss, why, and can we ultimately manipulate the same processes to make recovery more efficient? Finally, we know that the response to sleep loss changes with age, but we know little of the nature of this change. We do not know why this change occurs, and do not know the underlying neural correlates of this change. This is particularly important as any strategies employed to manage sleep loss or manipulate the recovery process may help young adults but hurt old adults. Sleep loss is pervasive throughout society, but the effects of sleep loss may not be the same in all individuals. Better understanding of how sleep loss affects us on an individual basis is critical to the management of sleep loss at a societal level. Since aging appears to be a factor at a behavioral level, it seems reasonable to assume it would be a factor on a neural level. Understanding how age affects the response to sleep deprivation and recovery at a neural level will be critical in furthering our understanding of how sleep loss affects the brain, and futher inform us as to whether alternate strategies may be

necessary to manage the effects of sleep loss in old adults. I will attempt to address some of these questions in the chapters to follow.

Specifically, the first chapter will focus on the effects of sleep loss on endogenous attentional orienting. This is a process that requires utilization of predictive information and generation of an adaptive attentional bias towards a specific location in space. Sleep deprivation has been shown to impair this ability, but the neural correlates of this effect are unknown (Gunter et al., 1987; McCarthy & Waters, 1997). The task utilized in this study has been well validated, and the neural correlates of this process are well identified over a number of studies. This analysis will attempt to examine the effects of sleep loss on posterior cingulate and parietal functioning, regions associated with endogenous attentional orienting. With respect to this task, posterior cingulate cortex (PCC) has been implicated in the processing of spatial cue information (Hopfinger, Buonocore, & Mangun, 2000; Hopfinger et al., 2001; Mesulam et al., 2001; Small et al., 2003). The effect of sleep loss on this attentional process is examined in detail.

The second chapter will focus on the effects of age and sleep loss on frontal functioning. It is known that both age and sleep loss affect the frontal cortex. It is telling that independently of each other, sleep loss and aging scientists both developed a theory of frontal lobe susceptibility explaining much of the performance impairments. More than anything, this is suggestive of frontal lobe functioning, i.e. the frontal lobes may be particularly sensitive to a variety of stressors. Old adults show a higher incidence of sleep problems and impaired sleep quality even in the absence of sleep problems. Taken together, these data spell a potentially disastrous outcome for sleep-deprived old adults.

These data suggest that old adults may be more likely to experience sleep loss, and that they may handle sleep loss differently than young adults. This is of particular importance as, to date, little is known about the response to sleep loss in old adults. Most studies of sleep loss have been conducted in young adults, and to my knowledge, no studies have examined the interacting effects of age and sleep loss on brain function using functional imaging techniques. Examination of this is critical, as the data from young adults may not generalize to an older population. Since both age and sleep loss may preferentially affect frontal functioning, a task targeting frontal function was selected for this study. This task is a variant of a go/no-go task previously described (Garavan et al., 1999), and it contains components of distinct cognitive abilities that rely on distinct frontal networks, i.e. response inhibition, response selection, and error processing. The effect of sleep loss, age, and their interaction on these abilities and simple motor output are examined in detail.

The third chapter will focus on neural and performance recovery from sleep deprivation in old and young adults. Data on both neural and performance recovery is sparse. Even less is known regarding age differences in the process of recovery. Given that recovery sleep is less intense in old than young adults suggests that there may be a differential response to recovery of performance. If there is not, then there must be a change in the relationship between variables of recovery sleep and subsequent performance. The response to recovery sleep, in terms of performance and brain activity, is examined in detail. Relationships between sleep variables and performance and brain activity will be explored.

Chapter four will focus on the ability to predict the response to sleep deprivation and recovery using baseline brain activity, as well as examining relationships between performance and change in brain activity across conditions. This is particularly important, as understanding why some individuals are more resilient in the face of sleep loss and why some recover from the effects of sleep loss more quickly may shed light on how sleep loss causes performance deficits. Recent studies have explored this relationship, and have suggested that higher overall activation levels or increased fronto-parietal activation predicts preserved performance (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005). However, all of these studies have used working memory tasks. It is unclear whether these changes generalize beyond working memory tasks. A particular examination of regions associated with response inhibition will be explored.

A general discussion will follow these chapters, which will attempt to link these data with the literature. This will be done with particular attention to my theory of the neurobiology of sleep loss that I discuss below in the subsection 'To respond or not to respond: A neural model of the performance impairments of sleep loss'. This theory attempts to describe the neurobiology underlying two major performance impairments caused by sleep loss, i.e. errors of omission and commission. Ultimately, these impairments are recorded on cognitive tasks, and cognitive tasks have limited relevance to performing real world jobs. Real world jobs generally require the functioning of a variety of cognitive abilities, each of which may interact and compensate for impairments in others. Cognitive tasks, on the other hand, strive to isolate distinct cognitive abilities in order to ascertain their link to neural systems. In the case of this dissertation, we

employed the use of an attention shifting task and a motor response inhibition task. These tasks target abilities that are pervasive throughout our daily activities, and come into play whenever learned any decision to act is made. A flashing light on the side of the road suggesting that children may be crossing the road would trigger a visual search for any children that might be crossing the street. A red light that suggests taking the foot off the gas pedal and putting it on the brake pedal would trigger an inhibition of the more common action of pressing the gas pedal to switch to a different pedal that is more appropriate in the context. In light of examples such as these, it is easy to see how impaired attention shifting or inhibitory functioning could lead to an increased risk for accidents which is one of the major reasons why we care about the effects of sleep deprivation on performance.

On the use of functional magnetic imaging for sleep deprivation studies

Studies of sleep and sleep loss have benefited from thorough behavioral and physiologic measurements. Since the 1930s, use of EEG has informed our understanding of neurophysiologic changes that are associated with sleep deprivation. Even before that, so did molecular and anatomical studies of the brain in humans and animals. However, these techniques have limited spatial resolution, and are often limited in focus to particular *a priori* regions of interest. Functional imaging techniques are particularly useful for the examination of changes in brain activity throughout the brain. Early studies used positron emission tomography (PET) to study sleep deprivation, but this too has limitations. PET imaging can be used to study a variety of processes depending on

the radionuclide injected. Popular uses measure glucose utilization and glucose metabolic rate using flourodeoxyglucose (FDG) injections, or oxygen flow and consumption using injections of oxygen-15. The advantage of PET imaging is that it can measure absolute changes in each of these measures throughout the whole brain. However, the temporal resolution of PET is poor, being on the order of an hour for FDG PET and two minutes for oxygen-15.

Functional magnetic resonance imaging (fMRI) utilizing the blood oxygen level dependent (BOLD) method has a superior temporal resolution in comparison with PET methods. The technique was first described by Ogawa and colleagues in 1990, and is based on measuring changes in the proportion of deoxyhemoglobin to oxyhemoglobin (Ogawa, Lee, Kay, & Tank, 1990). Deoxyhemoglobin is paramagnetic and thus can be detected when placed within a magnetic field by the perturbations it creates. This is an indirect measure of neural activity, as it relies on the coupling of tissue oxygenation with local neural activity. Thankfully, through a series of animal studies, this coupling has been confirmed in a variety of circumstances (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis & Pfeuffer, 2004; J. K. Thompson, Peterson, & Freeman, 2003). BOLD changes are most tightly coupled to changes in local field potentials which are representative of activity within populations of neurons (Logothetis et al., 2001). Simply put, it is assumed that the cognitive demands of a task will cause a change in neural activity within local populations of neurons. This change in neural activity will trigger local oxygen recruitment, which will result in a change in the oxyhemoglobin to

deoxyhemoglobin ratio. This will lead to changes in the perturbation of the magnetic field, thus giving an indirect measure of neural activity.

With this method, whole brain scans can be acquired on the order of seconds, and no radioactive injection is required. This means that whole brain measurements can be obtained on the order of seconds, and that this method can be repeated within an individual indefinitely without obvious health consequences (assuming the technique is used correctly and screening is adequate). However, fMRI is based on changes in the magnetic properties of blood flow, and thus absolute measures cannot be obtained. Any change in the state of the brain on a holistic level may confound results. This is particularly worrisome for sleep research when one notes the observations of Hammond (Hammond, 1865), which suggests that blood oxygenation in the brain changes dramatically and globally in the transition into sleep. This change is so dramatic that it is observable to the naked eye, resulting in an overall change in brain surface color and an increase in the distance between the brain surface and the skull. Thus, fMRI studies of sleep/wake transitions may need to account for this global change. This may also be important for the study of sleep loss as well, and may require careful consideration when interpreting results. This point is addressed in the fMRI analysis section of the Methods with the use of Macey's algorithm to remove global confounds (Macey, Macey, Kumar, & Harper, 2004). However, it seems unlikely that this affect observed by Hammond would be present in awake, sleep-deprived individuals, as any waking period was associated with a similar level of oxygenation (Hammond, 1865).

Functional imaging measures are indirect, depending on the coupling of neural activity to the specific measure employed in the technique. Nonetheless, the use of these methods has proven to be reliable under a number of circumstances and states. Functional MRI was chosen for the studies presented in this report for a number of reasons. First of all, this technology is accessible, and fairly safe, and is relatively inexpensive. Secondly, the temporal resolution of fMRI is superior to many other methods. This, I find, is critical to the study of sleep deprivation. When an individual is in a sleep deprived state, they are in an 'unstable state' as Saper and Dinges have put it (Doran et al., 2001; Durmer & Dinges, 2005; Saper et al., 2001). Thus, one second an individual could be awake, and the next second that individual could be asleep. The most reproducible behavioral change observed following sleep loss of any kind is an increase in response variability. This suggests that brain states and behavioral states are increasingly unstable and heterogeneous the longer an individual is awake. This very notion has been described for roughly 50 years, and observed for over a hundred (Bjerner, 1949; Patrick & Gilbert, 1896; Williams et al., 1959). PET measurements suffer from poor temporal resolution, which will lump all brain activity over an hour long period into one measurement, or at best over a two minute period. If one wishes to separate and examine separately states of good and poor performance, and their neural correlates, then one will need a method with superior temporal resolution. Additionally, if one wishes to separately examine the neural correlates of distinct cognitive events, one will also need superior temporal resolution. For these reasons primarily, fMRI was chosen, for it offers reasonable temporal resolution and excellent spatial resolution. The

use of this method allowed us to examine regional changes in brain activity associated with distinct cognitive events in relation to changes in sleep condition and age.

To respond or not to respond: A neural model of the performance impairments of sleep loss

Sleep loss, amongst a constellation of consequences, results in alterations in subjective experience and impairments of objective performance. This is presumably because extended wakefulness somehow alters brain physiology. Though this is an obvious assertion, pinning down exactly "how", "where", or, perhaps more importantly, "why" has proved troublesome. The numerous tasks that have been used to determine how sleep loss affects brain function have provided numerous, complicated, and at times conflicting, results. One of the main consistencies in functional imaging studies of sleep loss is that results are inconsistent across task type. This is not a surprising finding, as the effects of sleep loss on performance depend on task type as well (Frey et al., 2004; Van Dongen et al., 2004). Despite this, there are a few consistent changes across task type, i.e. regions of cortex that change their activity patterns with sleep loss for a variety of tasks. Two that are of particular importance are parietal cortex and left frontal cortex (Bell-McGinty et al., 2004; Chee & Choo, 2004; Drummond & Brown, 2001; Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001). Over-recruitment or preserved recruitment in these regions on tasks of verbal learning, divided attention, working memory, and logical reasoning appear to preserve performance levels after sleep

deprivation (Bell-McGinty et al., 2004; Chee & Choo, 2004; Drummond & Brown, 2001; Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001).

Therefore, it may be possible to reframe these data to form an alternate hypothesis. The reason that there are differences in the response to sleep deprivation depending on task type is because sleep loss alters brain function differentially throughout the brain. More specifically, tasks that target neural networks more susceptible to sleep loss will show greater performance impairments than those that target neural networks that are less susceptible. Thus, the response to sleep loss would not depend on task type, per se, but instead on the interaction between sleep promoting mechanisms, wake promoting mechanisms, and the susceptibility of the neural networks required to perform the task to the influences of these sleep/wake mechanisms.

It has been proposed that extended wakefulness leads one into an unstable state whereby the individual is flip flopping in and out of NREM sleep and wake states (Doran et al., 2001; Saper et al., 2001). Recent data support this idea, by showing that lapses occurring after sleep deprivation differ from lapses occurring in the rested state (Chee et al., 2008). Specifically, these lapses involve the dampening of neural responses within the visual cortex, thalamus, and inferior parietal cortex. These data suggest lapses occurring after sleep deprivation are more likely to be caused by gating of information to the cortex and visual attention to that information, i.e. the brain is not processing the environment. This seems in line with the idea that these lapses could represent microsleeps defined as brief transitions into NREM sleep states. If this hypothesis is true, neural network susceptibility to sleep loss may depend on regions that show the greatest

suppression of activity following transition into NREM sleep. This is especially plausible if one considers that a transition into NREM sleep not only suppresses activity in a number of cortical regions, but breaks down the effective connectivity between them (Massimini et al., 2005). A common finding among PET studies of sleep is that lateral and medial frontal, inferior parietal and parieto-temporal, and cingulate activations are reduced in NREM sleep (Braun et al., 1997; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). These regions subserve a series of higher order cognitive abilities involving attention, working, episodic, and semantic memories, language, contextually dependent behaviors, and motivational and emotional processing (Cabeza & Nyberg, 2000; Critchley, 2005; Mesulam, 1981, 1986, 1998). These cortical regions are all higher order multimodal and transmodal association areas that, through their interaction with each other, integrate sensory information and transform it into conscious experience (Mesulam, 1998). Many of these neurobehavioral functions are affected by sleep deprivation (see above section 'Sleep, Sleep loss and objective performance'). Because they are so critical to these complex behaviors, multimodal and transmodal association areas may be among the most active and receptive to neural plasticity during the day and thus may require more attention during sleep. It has been shown, recently, that synaptic potentiation occurs predominantly (if not exclusively) during periods of wakefulness (Vyazovskiy et al., 2008). This build up of synaptic weights increases energy demands, and, if left unchecked, the energy demands may exceed what the body can provide. Tononi's data suggest that slow waves propagate throughout the cortex, particularly within lateral association cortex (fronto-parietal predominantly, (Massimini

et al., 2004)). As this occurs, Tononi's model of synaptic downscaling suggests the signal to noise ratio is preserved, even improved, while energy demands are reduced (Tononi & Cirelli, 2003, 2006). This hypothesis is elegant, for it accounts for energy demands, learning effects, and provides a potential reason for the homeostatic drive and why adenosine, a molecule tied strongly to metabolism, is so implicated in that drive.

When sleep-promoting mechanisms override wake-promoting mechanisms during lapses, it may be these multimodal and transmodal association areas that are suppressed to the greatest degree. Therefore, two primary errors should be expected due to sleep deprivation. One error type would involve the complete lack of behavioral responses due to total disengagement from the environment, i.e. lapses or microsleeps. These errors would occur, because the individual is functionally asleep, or at least is not processing sensory input. The individual is completely and totally disengaged from the environment. However, this effect is intermittent, and it has been shown repeatedly that errors can occur even when an individual is awake and responding.

I hypothesize the other error type would involve slowed or inappropriate responding, even while the individual is awake and responding and processing sensory input. This type of error is heterogeneous and highly dependent on task type. However, I would still like to argue that these heterogeneous errors occur for a similar reason. These errors would all be due to the intermittent suppression of higher order cortical association areas subserving the requisite contextually dependent abilities, e.g. errors of commission due to prefrontal inefficiency. An alternative interpretation is that upon realization of the actual increase in performance lapses, individuals over-compensate by ramping up

responses. This explanation does not appear to be ideal, as response times do not necessarily speed up during the periods sleep-deprived individuals are awake. Thus, something more fundamental must be occurring that involves processing within association cortex. This could be inefficiency of processing in these cortical regions due to intermittent suppression, or due to intermittent break down of cortical effective connectivity.

If this proposed model is correct, these two general error-types should be neurologically distinct, with the latter being more neurologically heterogeneous and task dependent. The former would be more due to total disengagement from the environment and engagement of sleep mechanisms, and should depend more on sustained attention and arousal-related processes. Indeed, a hallmark of extended wakefulness is the suppression of EEG alpha wave amplitude and delta wave intrusion, which predicts the onset of lapses (Bjerner, 1949; Williams et al., 1959). The second error type would be more due to inefficient processing within networks associated with the tasks due to the intermittent suppression of these regional activities during lapses. As the severity and number of lapses increases, the risk for the second type of error should increase as well, as this would potentially increase the instability of processing within these regions of association cortex. Indeed, with increasing sleep deprivation, the prevalence of errors of omission is correlated with the prevalence of errors of commission (Doran et al., 2001).

In addition to these regional suppressions in activity due to sleep loss, compensatory responses leading to increased recruitment of distinct brain regions would occur. Some of these would be task related, and some not. Task irrelevant increases in

activation should primarily be due to ramping up attentional and arousal regions, either directly through activations within the attention network (see above) or indirectly through increasing activity in motivation-related regions that could increase arousal. Saper has suggested that one of the cortical inputs into the VLPO comes from cingulate inputs, which is often associated with motivational processing (Chou et al., 2002). This compensatory recruitment may improve performance beyond reducing lapses simply by reducing the intermittent suppression of association cortex by suppressing VLPO activity. Task relevant regions recruited would presumably be dependent upon the task performed, and would preserve performance, but only for performance measures specifically associated with the task at hand, i.e. recruiting these regions should not reduce lapses per se. What complicates matters further is that these two sets of compensatory mechanisms would necessarily interact. Thus, though globally errors of omission and commission would correlate with each other, the degree to which they correlate should vary between individuals. For example, one individual may have larger stores of attention-related processing but smaller task-specific compensatory resources. This would mean that individual would have fewer lapses, following sleep deprivation than many other individuals, but when these lapses did occur, the likelihood of performance resulting in an error of commission would be relatively higher. In the opposite case, an individual may have smaller attentional stores and larger task specific resources. In this case, lapses would be more likely to occur, but due to the larger task specific stores, the likelihood of performance resulting in an error of commission would be relatively lower. Therefore, individual variability in terms of vigilance and arousal-related resources may explain the

larger part of performance variance, but independent, task specific resources should explain an important distinct part of the performance variance. Therefore, the response to sleep loss should vary among individuals, because neural resources underlying those responses should vary among individuals. Where some of these resources may be inherent to an individual, it is possible that some of these neural resources may be trained. It seems most likely that of the compensatory mechanisms, the general, arousal-related resources would be more dependent upon genetic traits, as Van Dongen's data suggests (Van Dongen et al., 2004). However, task-specific resources would most likely be due to an individual's personal experience and training in that task. The more one trains in a task, the more automatic the response. It has been shown that automatic responding is less impaired by sleep loss than responding that requires careful and novel deliberation (Harrison & Horne, 1999, 2000a; J. A. Horne, 1988). This may reflect an increased cognitive reserve among individuals with practiced experience with a given task, which is unavailable to those who are untrained.

In conclusion, sleep loss results in performance errors; however, it remains unclear why this occurs. I propose that sleep loss results in rapid and intermittent transition into NREM sleep due to excessive sleepiness. These rapid transitions will appear behaviorally as microsleeps or lapses. However, though these affect performance directly, their occurrence will also affect performance indirectly in periods where lapses do not occur. This is because of the underlying neurobiology of NREM sleep transition, which suppresses activity of much of association cortex and alters connectivity within association cortex, particularly within the frontal cortex. The ability to cope with these

effects will be dependent on both trait-like resources related to arousal and attention, and the level of training on the task at hand that the individual has received. These coping mechanisms should manifest neuronally as increased activity of new or previously recruited brain regions and maintained or increased connectivity between brain regions.

Methods

This dissertation examines data from two distinct studies. Data presented in chapter 1 comes from study 1, and data presented in chapters 2-4 comes from study 2. Methods of study 1 are presented first and methods for study 2 are presented following the study 1 section. The condition labels used below 'SO' (sleep opportunity) and 'Sd' (sleep deprivation) are not canonical of the literature. However, they are important, because when examining old adults it remains unclear if their sleep is 'normal' per se or if their sleep leads to so called 'rested wakefulness'. The only declaration we can make regarding old adults is that they are given the same opportunity to sleep. The denotation of Sd was chosen to more clearly distinguish it from the SO label visually. Thus, for the sake of consistency, study 1 and study 2 uses the label SO to refer to a 'sleep opportunity' condition which is similar to a condition of 'rested wakefulness' (RW) as reported in the literature. Further, Sd will refer to a 'sleep deprivation' condition, which is similar to a condition of 'continuous wakefulness' (CW) and sleep deprivation (SD), and total sleep deprivation (TSD) as reported in the literature.

Study 1
Study participants

Seven young, healthy adults (19.5±2.3 years, 3 female) participated in the study. Participants were screened with questionnaires and in person interviews and no subject had a history of significant medical, neurological, or psychiatric illness. These

questionnaires included the mini-mental state examination (MMSE), the Pittsburgh sleep quality index (PSQI), the Berlin questionnaire, and the Horne-Osteberg scale (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Folstein, Folstein, & McHugh, 1975; J. A. Horne & Ostberg, 1976; Netzer, Stoohs, Netzer, Clark, & Strohl, 1999). A score of 20 or less on the MMSE is considered indicative of dementia or cognitive abnormalities (Folstein et al., 1975). Any participant with a score below 20 was excluded from participation. A score greater than 5 on the PSQI is indicative of poor quality sleep (Buysse et al., 1989). Any participant with a score above 5 was excluded from participation. The Berlin questionnaire was used to prescreen for possible sleep apnea (Netzer et al., 1999). The Horne-Ostberg Questionnaire is used to assess morningness and eveningness preference (J. A. Horne & Ostberg, 1976). In order to avoid circadian confounds across subjects, 'neither types' were selected for this study, whom are subjects without a morning or evening preference. A score of 42 to 58 reflects 'neither types', with scores above 58 reflecting morning types, and scores below 42 reflecting evening types. All participants reported that they were right-handed. Their mean abridged Edinburgh handedness score was 57.1 ± 1.5 on a scale of -60 (left handed) to +60 (right handed) (Oldfield, 1971). All participants gave written informed consent, and this study was approved by the Institutional Review Board at Northwestern University.

Protocol

Study participants completed two visits to the General Clinical Research Center (GCRC) at Northwestern Memorial Hospital, Figure M.1. Before each visit, participants

were instructed to maintain a diary of their sleep-wake habits. Sleep habits were also monitored for 1-2 weeks prior to each GCRC visit using wrist actigraphy (Cambridge Neurotechnology, Cambridge, England). Participants were instructed to obtain an average of 7-8 hours of time in bed per night. The order of the GCRC visits was counter-balanced in a cross-over design with each participant acting as their own control. In the sleep opportunity condition (SO), subjects entered the GCRC on the evening before scanning, and spent 8 hours time in bed (23:00-07:00). Subjects were scanned in the afternoon, 10-12 hours after awakening, between 17:00-19:00 h.

In the sleep-deprived condition (Sd), participants entered the GCRC on the evening before sleep deprivation began, and spent 8 hours time in bed (23:00-07:00). Participants were allowed to leave during the first day between 08:00 - 17:00 h, but were instructed to remain awake and to avoid using caffiene. Wrist actigraphy recordings and sleep diaries were used to monitor participant compliance. Participants were instructed to log the occurrence of any sleep episodes or naps during the study period. Participants were also specifically questioned about naps, and none reported napping within the 3 days prior to scanning. Following 34-36 hours of continuous wakefulness, participants underwent functional MRI scanning. Participants were required to sleep for at least eight hours in the GCRC, to recover from sleep deprivation, before they were able to go home after scanning.

Prior to their first scanning session, participants were familiarized with the task during a training session in the psychophysics laboratory. Participants completed three training runs. There were 152 trials per run, which lasted just over 7 minutes. These data

were reviewed to make sure the subjects could perform the task. None of the participants failed to perform adequately during the training session. Details of the training environment have been previously reported (Mesulam et al., 2001; Small et al., 2003). Participants sat 40 cm away from a 21 inch monitor and used a chin rest to minimize head movements. The task was presented using superlab software running on a Macintosh computer (Apple, Cupertino, CA).

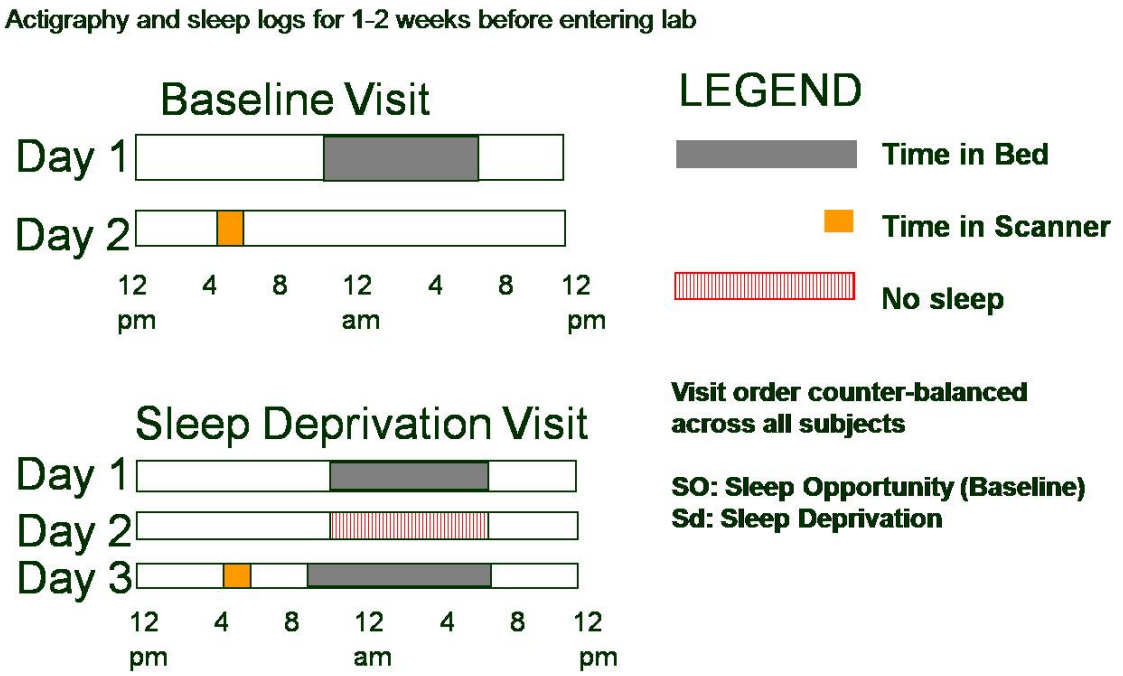

Figure M.1. Study 1 protocol. Study participants entered the general clinical research center (GCRC) on two separate occasions for a baseline visit and a sleep deprivation visit. The baseline visit consisted of a sleep opportunity (SO) condition and the sleep deprivation visit consisted of a sleep deprivation (Sd) condition. Condition order was counter-balanced across all participants. Solid gray bars represent periods of sleep in the GCRC, and the red unfilled bar represents a period where participants remained awake when they would normally sleep. Solid orange bars represent fMRI scans. Note that fMRI scans occured at the same time of day in both conditions. Participants were monitored continuously throughout the GCRC stay.

Data collection and analysis procedures

Behavioral tasks

The Posner Task

The Posner task used in this study was a variant of one developed by Posner for examining endogenously triggered shifts of spatial attention (Posner, 1980; Small et al., 2003). Figure M.3 illustrates trial organization and timing. Subjects were instructed to keep their eyes fixed on the central diamond throughout the experiment, and to respond to the appearance of targets "X" but not foils "+" in their peripheral vision. One-hundred milliseconds into a trial subjects saw a directional or non-directional cue. Directional cues involved the bolding of one-half of the central diamond, while non-directional cues, termed "neutral", involved the bolding of the entire central diamond. Directional cues that correctly indicated the side of target or foil appearance, were termed "valid" or informative. Cues that pointed opposite to the side of target or foil appearance were termed "invalid" or misleading. To avoid the generation of temporal expectancy, the time between the appearance of the cue and the appearance of the target (stimulus onset asynchrony or SOA) could be 200, 400 or 800 ms. The target (or foil) then appeared for 100 msecs, and was followed by a variable end-trial interval of 1700, 1500 or 1100 msec respectively, so that the total trial duration was always 2100 msecs. Trials with reaction times less than 100 ms or greater than 1000 ms were discarded. Reaction times less than 100 ms or responses to foils were considered "errors of commission" or false positives. Trials with no response or reaction times greater than 1000 ms were considered "lapses" or false negatives.

An event-related design was used. Subjects completed three experimental runs in each scanning session. Each experimental run contained 152 trials (138 targets and 14 foils), of which 66% were directional (valid or invalid) and 34% were non-directional (neutral). Valid cues made up 80% of all directional cues. Trials lasted for 2.1 seconds, and each run lasted seven minutes, Figure 1. Fifty null events were distributed throughout the run to allow deconvolution of the hemodynamic response function (HRF) (Burock, Buckner, Woldorff, Rosen, & Dale, 1998). Null events consisted of a fixation display for 2.1-6.3 seconds.

Behavioral analysis

Behavioral data collected within the scanner are reported. Total errors of commission and omission were calculated for each subject in each sleep state, and adjusted by the number of responses. Paired t-tests were used to compare these errors between sleep states.

Reaction times were examined using an ANOVA model that included fixed factors of sleep state (SO and Sd), trial type (valid, neutral, invalid), side (left, right) and SOA (200, 400, and 800) and a random factor of subject. Bonferroni corrected post hoc t-tests were used to determine specific significant effects.

In order to examine the effects of sleep state on the anticipatory biasing of attention, valid trials were categorized into those that conferred a cue benefit (V^+) from those that did not (V^-). It was assumed that the anticipatory biasing of spatial attention was present if reaction time to a valid cue was significantly faster (at least one standard

error) than the mean reaction time to neutral cues in the corresponding SOA for that run. A cue considered to confer a cue benefit was termed (V^+), and all trials that did not meet the (V^+) criteria were considered to show no cue benefit (V^-). Categorization of the valid-cue trial-type in this manner was done so that the fMRI signal could be compared among validly-cued trials that were identical except for the presence of an anticipatory bias. We have previously used this calculation as a measure of whether or not the predictive cue caused an anticipatory bias in spatial attention (Small et al., 2003). The percentage of valid trials categorized as V^+ for each sleep state was compared using a paired t-test. The number of lapses and false positive errors as a function of the number of responses was also compared across sleep states. All statistical analyses of behavioral data were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

As described previously, in study 2, one of our aims was to directly compare the effects of sleep deprivation on neural correlates of attention and cognitive control. Unfortunately, repeated testing of the Posner task in this study resulted in habituation in the response to cues, i.e. no cue benefit effects on reaction time were observed. Thus, effects of sleep deprivation on the neural correlates of the Posner task were not compared directly to that of the Go/No-go task. Future examinations of the Posner task will need to carefully limit subject exposure to avoid these habituation effects.

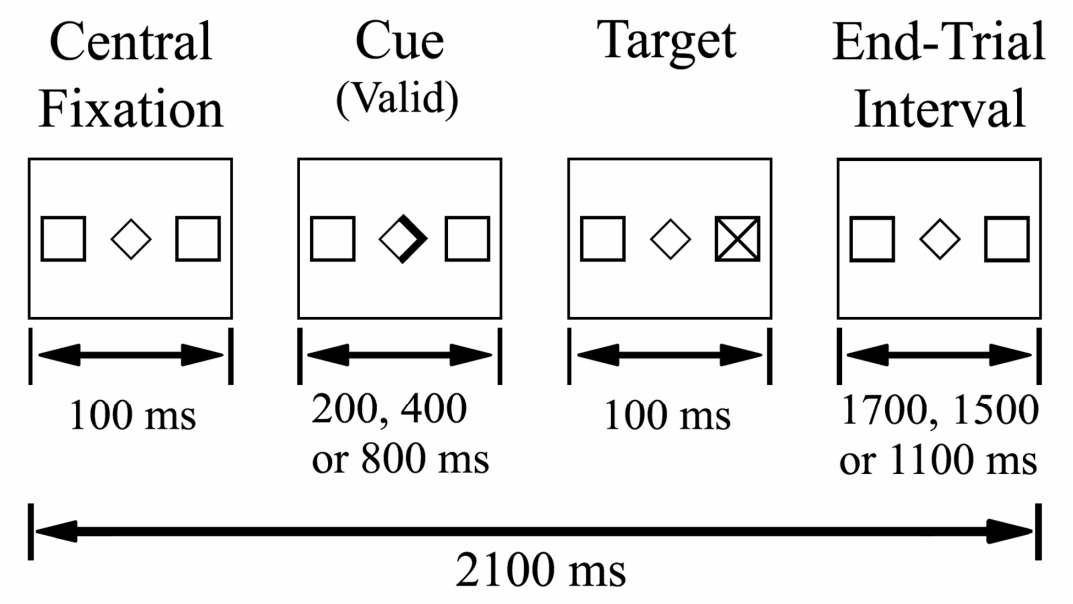

Figure M.3. Schematic representation of the Posner task, and the timing parameters of a single trial. An event-related design was used. Subjects performed three runs in the scanner in each session. Each trial consisted of fixation followed by a cue presented for 200, 400, or 800 msecs. Following the cue, the target was presented for 100 msecs. The intertrial interval varied as a function of the SOA length to maintain an overall trial length of 2100 msecs, matching TR length.

Functional imaging methods

MRI scanning

Subjects were imaged using a Siemens Vision 1.5-T scanner. Both anatomical (T1) and functional scans were acquired. T_1-weighted anatomical images were obtained using a 3D FLASH (fast low angle shot) sequence with an inferior saturation band to reduce flow artifacts. The T1 imaging parameters were [repetition time/echo time (TR/TE) 22 ms/5.6 ms, flip angle 25º, field of view (FOV) 240 mm, matrix 256 ×256, 160 slices with a thickness of 1.0 mm]. Anatomical scans were obtained in transaxial planes parallel to the anterior commissure-posterior commissure (AC—PC) line. Twenty-four contiguous 5-mm slices aligned to the AC-PC line ($3\times3\times5$ mm resolution) were acquired using a susceptibility-weighted single-shot EPI method in order to image the regional distribution of the BOLD signal (TR/TE 2100/40ms, flip angle 90˚, FOV 240, 64×64 matrix). In all functional runs, the MR signal was allowed to reach equilibrium over the six initial scans, which were excluded from analysis.

In the scanner subjects viewed images that were projected onto a nonmagnetic screen located approximately 170 cm from their eyes. Head movement was reduced by using a vacuum pillow (VacFix, Toledo, OH). Subjects responded using a fiber-optically linked button.

fMRI analysis

Data analysis of all fMRI data were conducted using the Statistical Parametric Mapping version 2 (SPM2) software packages (Wellcome Department of Imaging

Neuroscience http://www.fil.ion.ucl.ac.uk/spm) running in the Matlab environment (Mathworks, Inc., Sherborn, MA).

Chapter 1: Sleep deprivation alters functioning within the neural network underlying the covert orienting of attention

During data acquisition, the functional image data for one subject was lost. This subject was excluded leaving six subjects for the fMRI analysis. Functional data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience http://www.fil.ion.ucl.ac.uk/spm) running in the Matlab environment (Mathworks, Inc., Sherborn, MA). Functional images were preprocessed as previously described (Small et al., 2003). Functional images were slice time corrected, realigned and coregistered to the anatomic T1 volume. The T1 volume and functional images were normalized to the MNI-305 template supplied with SPM2. The template approximates the space described in the atlas of Talairach and Tournoux (Tailairach & Tournoux, 1988). Functional images were smoothed with a 7 mm Gaussian kernel.

In order to minimize the effect of head movements on the analyzed BOLD signal, trials occurring during the 16 seconds preceding any head movements over 1mm were "excluded" by modeling them as an effect of no interest. Only trials that preceded a movement were modeled this way because movements instantaneously disrupt the measurement of BOLD signal by shifting voxel positions. The effects of movements are immediate as motion effects are not filtered by the hemodynamic response as is the case for neural activity (Babkoff, French, Whitmore, & Sutherlin, 2002; Barch et al., 1999;

Small et al., 2004). Residual movement-related variance was further modeled by including affine movement parameters in the design matrix.

As in our previous studies, only valid trials (i.e., trials with valid cues) were analyzed (Gitelman et al., 1999; Mesulam et al., 2001; Small et al., 2003). Specifically, BOLD responses were examined for contrasts between V^+ and V^- trials in Sd and SO states. Although there are fewer trials in the Sd state due to the increase in lapses, there were still at least 130 valid responses per subject.

The fMRI design matrix did not include a global covariate, as it can bias the parameter estimates (Aguirre, Zarahn, & D'Esposito, 1998). Instead, a voxel-level linear model of the global signal (LMGS), which has been shown not to introduce bias, was used to remove the global effects (Macey et al., 2004).

Group activations were assessed by a random effects analysis. However, one concern with having only 6 subjects in this study is that the low degrees of freedom might violate assumptions underlying parametric statistics used to analyze the fMRI data. By smoothing at more than double the normalized voxel size (7 mm^3 for 3 mm^3 voxels) the assumptions underlying voxel-level statistics should be preserved (Friston, Holmes, Poline, Price, & Frith, 1996). However, under low degrees of freedom the random field distributional assumptions underlying cluster level statistics may still be violated. Cluster-level p-values depend on the statistical smoothness of the image, measured in RESELS (resolution elements) at each voxel, and the consistency of this smoothness or stationariness across the image (Worsley et al., 1996).

SPM uses the average RESELS per voxel (RPV) value for calculating cluster statistics. Under lower degrees of freedom, however, this value is more likely to vary across the image. Regions that have fewer RESELS per voxel than the average used by SPM are considered smoother, and have a greater probability of containing larger clusters. False positive clusters are more likely to occur in these regions. Conversely, areas of an image that have more RESELS per voxel than average are rougher, and less likely to contain false positive clusters (Hayasaka, Phan, Liberzon, Worsley, & Nichols, 2004).

In order to reduce the chance of a Type I error, mean RPV values were calculated for each cluster passing the cluster-height threshold of $p < 0.05$ corrected for multiple comparisons across the brain. RPV was then transformed to the more intuitive measure of smoothness, full width at half maximum (FWHM), using the relationship $FWHM = RPV^{(-1/3)}$. This value was expressed in mm by multiplying by the normalized, isotropic voxel size of 3 mm. Clusters with a mean FWHM larger than the one used by SPM (larger FWHM is equivalent to smaller RPV), were designated as non-significant because of the greater chance of a false positive cluster in these regions.

In order to better visualize the BOLD responses within the PCC and the IPS, BOLD signal time courses from the most significant voxels in the PCC and the IPS were extracted for both sleep states and transformed to peri-stimulus time histograms (PSTH).

Confirmatory analyses

In order to determine if V^+ and V^- categorization reflected true effects of cue benefit two additional analyses were performed. Functional data were analyzed using SPM2 (Wellcome Department of Imaging Neuroscience http://www.fil.ion.ucl.ac.uk/spm) running in the Matlab environment (Mathworks, Inc., Sherborn, MA). Functional images were preprocessed as described above

As in our previous analysis, only valid trials (i.e., trials with valid cues) were analyzed. Two additional analyses were conducted. Firstly, Cue Benefit Scores (CBS) were calculated as previously described (Small et al., 2003). The equation below shows how cue benefit scores were calculated for each valid trial. Essentially, the log of an individual reaction time for a given valid trial is subtracted from the log of the mean neutral reaction time matched to the valid trials SOA. This is then divided by the log of the mean neutral reaction time matched to the valid trial SOA.

$$CBS_i = 100 \times \left(\frac{\left(\frac{1}{N} \sum_{n=1}^{N} \log_{10} RTN_n \right) - \log_{10} RTV_i}{\frac{1}{N} \sum_{n=1}^{N} \log_{10} RTN_n} \right)$$

CBS scores were then included as a parametric regressor within each subject's first level model. CBS contrast images (for both positive and negative correlations) were then forwarded to the second level for random effects analysis.

Secondly, BOLD responses were examined for contrasts between V^+ and V^- trials in SD and R states as described above but for one exception. In this analysis, V^+ and V^- categorization was based on mean invalid reaction times minus one standard

error. To determine if the results in these contrasts were similar to the original analysis method, PCC and IPS 10 mm regions of interest were chosen centered on the locus of activation of the original V^+ and V^- analysis. Activations in these regions were significant, corrected across the entire region of interest. All other activations were significant corrected across the entire brain volume.

Study 2

Study participants

Nine young adults (26.0±1.2 years, 4 female) and nine old adults (67.6±2.0 years, 5 female) participated in the study. No participant had a habitual intake of caffeine greater than two cups of coffee per day or equivalent, and no greater than seven drinks of alcohol per week. All participants were screened with questionnaires, interviews, and polysomnographic (PSG) recordings and had no history of significant medical, neurological, or psychiatric illness. These questionnaires included the mini-mental state examination (MMSE), the Pittsburgh sleep quality index (PSQI), the Epworth sleepiness scale (ESS), the Berlin questionnaire, and the Horne-Ostberg scale (Buysse et al., 1989; Folstein et al., 1975; J. A. Horne & Ostberg, 1976; Johns, 1991; Netzer et al., 1999). A score of 20 or less on the MMSE is considered indicative of dementia or cognitive abnormalities. Any participant with a score below 20 was excluded from participation (Folstein et al., 1975). However, our participants were high-performing, and all subjects scored 27 or higher on the MMSE (mean young 29.9±0.1; mean old 29.1±0.5). A score greater than 5 on the PSQI is indicative of poor quality sleep (Buysse et al., 1989). Young and old participants did not differ significantly on PSQI scores, and averaged

below 5 (mean young 2.3±0.5; mean old 3.8±0.7, p = 0.107). However, they did differ on subjective reports of habitual sleep duration (component 3 score; mean young 0.1±0.1 [7.7±0.05 hrs/night]; mean old 0.9±0.2 [6.8±0.12 hrs/night], $t_{16} = -3.396$, p = 0.004). This is significant after Bonferonni correction for multiple comparisons (8 comparisons: 1 global PSQI score, 7 component PSQI scores). It is important to note that this component is not a measure of time in bed, but a subjective measure of 'actual hours of sleep' each night. As reported in chapter 2, habitual time in bed was similar in both age groups. A score of 10 or more on the ESS is considered indicative of excessive sleepiness (Johns, 1991). Young and old participants did not differ between levels of subjective sleepiness, and averaged below 10 (mean young 5.6±1.1; mean old 6.1±1.5, p = 0.953). The Berlin questionnaire was used to prescreen for possible sleep apnea (Netzer et al., 1999). The Horne-Ostberg Questionnaire is used to assess morningness and eveningness preference (J. A. Horne & Ostberg, 1976). In order to avoid circadian confounds across subjects, 'neither types' were selected for this study, whom are subjects without a morning or evening preference. A score of 42 to 58 reflects 'neither types', with scores above 58 reflecting morning types, and scores below 42 reflecting evening types. There was a statistical difference in morning/evening preference across subjects (mean young 46.6±1.2; mean old 50.3±1.3, $t_{16} = -2.12$, p = 0.0498). However, both groups were neither types, and though there is a statistical difference, it is subtle and unlikely to bias further results. To screen for possible mood disturbances, the Beck depression index (BDI) was used for young adults and the geriatric depression scale (GDS) for old adults (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Yesavage et al.,

1982). A score of 9 or less on both of these scales is considered normal; subjects with scores higher than 9 on either scale were excluded (mean young 2.0±0.6 on the BDI, and mean old 2.9±0.9 on the GDS).

Old adults were healthy community dwelling individuals with no history of neurologic or psychiatric problems and were recruited through the Alzheimer's Disease Center Clinical Core registry at Northwestern University, where they received further screening. Participants, young and old, were additionally recruited through flyers and word of mouth. Old adults not recruited through the Alzheimer's Disease Center Clinical Core registry at Northwestern University still underwent the same screening procedures before entering the study. These adults were cognitively normal, performing within two standard deviations of normative scores on all tests within a comprehensive neuropsychological battery consisting of the Logical Memory subtest of the Wechsler Memory Scale – Revised (WMS-R) (Wechsler, 1987); the Consortium to Establish a Registry for Alzheimer's Disease Battery (CERAD) (word list learning, recall, and recognition, and constructions subtest) (Morris et al., 1989); the Trail Making Test, Parts A and B (Reitan, 1958); the Visual-Verbal Test (Feldman & Drasgow, 1959), and the Mini-Mental State Examination (MMSE)(Folstein et al., 1975).

Participants reported being right-handed with a mean Edinburgh handedness score of 86.3 ± 3.6 for the young and 89.4 ± 5.7 for the old adults on a scale of -100 (left handed) to +100 (right handed) (Oldfield, 1971). All research participants gave written informed consent, and this study was approved by the Institutional Review Board at Northwestern University.

Protocol

Study participants were admitted to the General Clinical Research Center (GCRC) on two separate occasions, completing Sleep Opportunity (SO), Sleep Deprivation (Sd), and Sleep Recovery (SR) conditions, Figure M.2. Sleep was monitored for 1-2 weeks before each GCRC visit using sleep logs and wrist actigraphy (Mini Mitter, Bend, OR) to ensure that participants had complied with their self-reported sleep habits. These habits had to fulfill the following criteria: spend between 7-9 hours time in bed per night on average, bed time between 22:00 and midnight, and wake time between 05:00 and 09:00. These criteria were used to ensure that our study participants did not have residual sleepiness coming into the experiment. Additionally, these criteria ensured that the participants had fairly regular sleep wake habits and were neither overly advanced nor delayed in their sleep/wake rhythm. During this pre-study period, participants were instructed to abstain from caffeine and alcohol intake. During the study period, participants were not provided with access to caffeine or alcohol while in the GCRC in any condition. The order of each visit was counter-balanced in a cross-over design with participants acting as their own controls. On the first visit to the GCRC, every research participant underwent a full PSG to screen for the presence of sleep disorders. Participants were excluded if they had an Apnea/Hypopnea Index of ≥ 15. This was chosen, as previous reports suggest that cognitive impairments and sleepiness due to obstructive sleep apnea do not become apparent unless the AHI is ≥ 15 (Young, Peppard, & Gottlieb, 2002). This criterion was used for both young and old participants. Research participants awoke at the same time of day in all conditions and completed all scans at the

same time of day. These scans were conducted in the afternoon to early evening (between 16:00 – 18:00), which is a period during which the circadian rhythm of performance is at a peak (Dawson & Reid, 1997; Froberg, 1977; Kleitman, 1963; Wright et al., 2002). This was chosen so that performance impairments and changes in brain activation would be due primarily to homeostatic influences and not to the effects of circadian rhythms on performance and brain activity. This design has two primary effects: one, performance in the sleep deprivation condition is better than if tested at the circadian low points of early morning, early afternoon, or late evening; and two, baseline performance is not confounded with early morning circadian or sleep inertia effects. This maximizes performance in both cases and probably minimizes variability which will increase the power of the study. This also ensures that performance impairments are due primarily to homeostatic and not to circadian variation.

In the sleep opportunity condition, each subject entered the GCRC two evenings before scanning. Sleep was recorded during both nights using polysomnography (PSG). All participants were allowed nine hours time in bed (TIB) to sleep on both nights. This number was chosen instead of habitual sleep/wake amount in order to saturate the sleep drive so that all participants would be as rested as possible regardless of age. Additionally, sleep quality in the laboratory is sometimes worse than observed in a habitual sleep environment, particularly on the first night (H. W. Agnew, Jr, Webb, & Williams, 1966). Thus, extending sleep may worsen sleep efficiency, but it will maximize daytime alertness. Following the first night of sleep recording, participants were allowed to leave during the day and activity was monitored with wrist actigraphy.

Following the second PSG recording, participants remained in the GCRC until after scanning, and were constantly monitored to make sure they did not fall asleep. In the afternoon, 10-12 hours after awakening, each participant was scanned while performing a go/no-go task (Garavan et al., 1999).

In the Sd condition, each participant entered the GCRC on the evening two nights before sleep deprivation began. PSG recordings were completed for both nights, and participants were allowed nine hours time in bed. Following the first PSG recording, participants were allowed to leave during the day and activity was monitored with wrist actigraphy. Following the second PSG recording, participants remained awake within the GCRC for 38 hours, and were constantly monitored to make sure the participant did not fall asleep. During their time in the GCRC, subjects were allowed to watch television, read, and interact and play games with the research staff.

In the SR condition, following the Sd condition, participants were allowed 10 hours time in bed in the GCRC to recover from sleep deprivation. When designing this study, we decided to extend recovery sleep beyond the nine hours offered at baseline. Though it would have been more consistent to maintain a nine hour bed time, there were a number of reasons for why we determined extending sleep is better. First of all, sleep following extended periods of continuous wakefulness is more intense (Blake & Gerard, 1937; Kleitman, 1963; Patrick & Gilbert, 1896; Pieron, 1913). This effect may bleed into the morning, confounding performance with the effects of sleep inertia. Secondly, sleep deprivation causes a strong rebound in SWS, which can lead to a REM sleep rebound suppression effect (Borbely, 1982; W. Dement, 1960; Webb & Agnew, 1965). Since

REM deprivation can result in performance impairments as well, it is important to give the opportunity to recover from REM deprivation as well (W. Dement, 1960). A method of doing this is to extend sleep, so that REM sleep can occur when SWS pressure is minimal and circadian pressure for REM sleep is maximal (Borbely, 1982). Finally, since participants were released after one night, without an additional sleep period, it is ethically imperative to offer enough sleep to recover from most of the effects of sleep deprivation. In this way, the increased risk for sleep loss-dependent accidents is minimized. Since it has been shown that 8-9 hours may not be enough to fully recover from sleep loss, the sleep period was extended to 10 hours of sleep opportunity (Belenky et al., 2003; Borbely, 1982; Herscovitch & Broughton, 1981; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). This may reduce the power to detect residual performance impairments. However, should performance impairments persist, and should the prefrontal hypothesis be correct, it is expected that these residual performance impairments would stem from persisting differences in prefrontal activity. If this is not the case, then it will become necessary to reevaluate the prefrontal hypothesis of sleep deprivation. That is to say, if the prefrontal cortex is the most vulnerable to sleep loss, then one would expect it to be the last to fully recover.

It is crucial to maintain the same wake time in sleep deprivation effects as number of hours since waking impacts performance levels. Thus, sleep start time upon the recovery night was an hour earlier, in order to give an extra hour of sleep, yet maintain the same wake time. Since participants were kept awake for 38 continuous hours, it is unlikely that bed times one hour earlier will impact sleep onset or efficiency adversely.

In the afternoon, 10-12 hours after awakening, each participant was scanned while performing the same go/no-go task as the other conditions. During this 10-12 hour wake period, participants were monitored constantly to make sure they did not fall asleep before scanning.

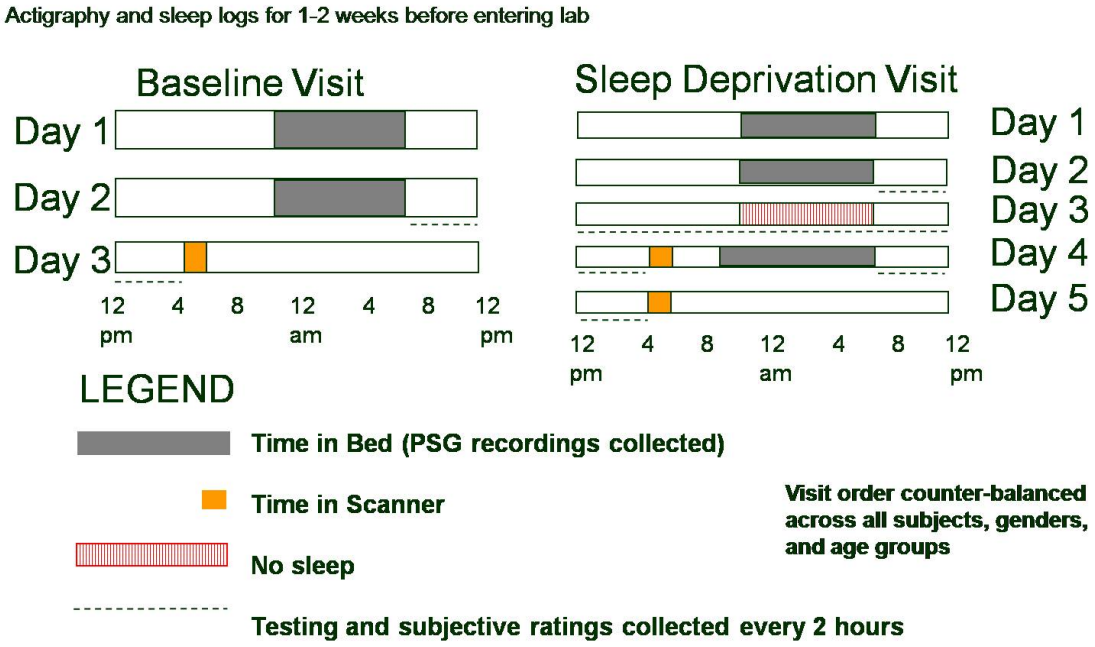

Figure M.2. Study 2 protocol. Subjects entered the general clinical research center (GCRC) on two separate occasions for a Baseline visit and a sleep deprivation visit. The baseline visit consisted of a sleep opportunity (SO) condition and the sleep deprivation visit consisted of a sleep deprivation (Sd) condition and a sleep recovery (SR) condition. Visit order was counter-balanced across all subjects, gender, and age groups. Solid gray bars represent periods of polysomnographic (PSG) recordings of sleep in the GCRC, and the red unfilled bar represents a period where participants remained awake when they would normally sleep. Solid orange bars represent fMRI scans. Note that fMRI scans occur at the same time of day in all conditions. Dashed lines represent cognitive testing and subjective ratings collected every two hours. Subjects were monitored continuously throughout the GCRC stay.

Data collection and analysis procedures

PSG recording and analysis

Sleep was monitored at the GCRC using PSG, including the placement of electrodes using the 10-20 system for monitoring central (C3,C4) and occipital (O1,O2) electroencephalogram (EEG) locations. Reference electrodes (A1,A2) were used for the C3/A2, C4/A1 and O2/A1 derivations. High filtering was set at 70 Hz and low filtering was set at a time constant of 0.3 s or 0.6 Hz. Sampling rate was set at 200 Hz. In addition, electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG) were obtained on all nights. Nasal/oral airflow, abdominal and chest belts, pulse oximetry and leg EMG was additionally monitored during the first habituation night to screen for the presence of sleep disorders. Signals were recorded via a paperless sleep recording system (Neurofax EEG-1100 Digital EEG Acquisition System, Nihon-Kohden), and scored visually according to the Rechtschaffen and Kales criteria (Rechtschaffen & Kales, 1968).

Each study participant had five nights of sleep recording. Two recordings occurred before each experimental visit (baseline visit 1 and 2 and sleep deprivation visit 1 and 2). These were all baseline nights with nine hours of time in bed. Baseline visit night 1 and sleep deprivation visit night 1 were considered habituation nights and these data were not examined due to the 'first night effect' (H. W. Agnew, Jr et al., 1966). This 'first night effect' represents impaired sleep quality and quantity due to sleeping in a new environment while wearing the sleep equipment. This effect is usually gone by night 2, but has significant effects on sleep during night 1 (H. W. Agnew, Jr et al., 1966). For all

analyses of sleep variables, baseline visit night 2 and sleep deprivation visit night 2 were averaged and used as sleep opportunity (SO) condition data. The fifth night was the night following sleep deprivation, and consisted of 10 hours of TIB. These were considered the sleep recovery (SR) condition data. Baseline and recovery characteristics for total recording time, total sleep time, sleep latency, sleep efficiency, percent of sleep period spent in wake, stage I, stage, II, slow wave sleep, and rapid eye movement (REM) sleep was analyzed and compared across age groups. Total recording time (TRT) was defined as the period between lights off and lights on. Sleep onset and morning awakening were defined as, respectively, the times of the first and last 30-sec intervals scored stage II, III, IV or REM. Total sleep time (TST) was defined as the time interval separating sleep onset from morning awakening minus the amount of time spent awake during the night. The sleep latency was defined as the time interval separating lights off from stage 2 onset. Sleep efficiency was calculated as the bedtime period minus the total duration of awakenings, expressed in percent of the bedtime period. Wake after sleep onset (WASO) was defined as the period of time spent awake after sleep onset and before lights on. Because the time in bed differed between conditions, percentage of stages I, II, III, IV, REM, and wake were scored and compared across age groups and absolute number of minutes in each of these stages was not analyzed. Stages III and IV were combined as slow wave sleep (SWS).

A two-way, repeated measures ANOVA was used to determine age (Young, Old), sleep condition (SO, SR), and age by sleep condition interaction effects on sleep characteristics. In Chapter 2 ‘Age alters the neural response to sleep deprivation within

the frontal cortex', only sleep data during the SO condition was examined. In this analysis, two-tailed, independent samples t-tests were used to determine age differences in sleep variables. All sleep data were analyzed using SPSS version 16.0 (SPSS, Inc., Chicago, IL) or Statistica 6.0 (StatSoft, Inc., Tulsa, OK).

Spectral analysis of PSG data

EEG data were analyzed using spectral analysis. This analysis was conducted on central (C3-A2; C4-A1) and occipital (O1-A2; O2-A1) EEG leads using an electrophysiological recording analyzer software package (PRANA, Phitools, Strasbourg, France). This software contains an automated artifact-detection algorithm which removes ocular, muscular, and movement artifacts which may confound spectral analysis. Following this automated procedure, individual records were visually inspected for verification of the procedure and removal of additional artifacts. These artifacts were treated as missing data, as simply eliminating the data may lead to spurious alterations of the EEG signal. Following artifact removal, a fast Fourier transform (FFT) was applied to the EEG signal at 2-second intervals, giving a frequency resolution of 0.5Hz. A Hanning window was used, minimizing the influence of the ends of each epoch on spectral analysis of frequencies. Power spectra from 15 consecutive 2-second epochs were averaged and matched to each 30-second visually-scored epoch. Spectral analysis was conducted at four distinct frequencies: delta (0.5-4.5 Hz), theta (4.5-8.5 Hz), alpha (8.5-12.5 Hz), and sigma (12.5-15.5 Hz). Total power was calculated over the combined frequency range (0.5-15.5 Hz), and relative measurements for each spectral frequency

were expressed as a percentage of the total power for each 30-second epoch. In the current report, data are presented for central EEG leads only (C3 and C4). These data are reported separately in chapter 3.

Since the first night effect may impact spectral properties of the EEG, baseline visit night 1 and sleep deprivation visit night 1 were not analyzed. Spectral analysis was conducted on baseline visit night 2, sleep deprivation visit night 2, and the recovery sleep night in all subjects. In order to measure the time course of the 'dissipation of the sleep drive' (Borbely, 1982) in young and old adults, a slope was calculated from logarithmic transformation of EEG delta power density (0.5-4.5 Hz) during hourly averages of NREM sleep periods across the time in bed. The same method was used to calculate the slope of sigma power across the night. Hourly averages of delta, theta, alpha, and sigma power density were calculated during NREM sleep periods across the first eight hours in both conditions. This allowed for an equal time in bed comparison between baseline and recovery sleep nights. Nine hours was not used as some subjects did not remain asleep during the final hour in the baseline condition. One young subject did not have any NREM sleep during the seventh hour of the recovery night, instead remaining in REM sleep for over an hour. In order to get a measure of NREM spectral power in this subject, the seventh hour was skipped and the eighth and ninth hours were used instead. This made it possible to include the subject in all repeated measures ANOVA analyses. For this young subject, the spectral power values for the sixth and the eighth hours did not differ by more than 10 μV^2. For delta power, mean REM delta power was subtracted from NREM delta power values to remove artifactual delta power. All these data were

compared using a three-way repeated measures ANOVA with time and sleep condition being within subject factors and age group being a between subject factor. The current report presents only data for spectral power in the delta and sigma frequency bands. All spectral data were analyzed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

Behavioral tasks

Go/No-Go Task

The task used in this study was a variant of one developed by Garavan and colleagues for examining prepotent response inhibition (Garavan et al., 1999). However, it was specifically constructed to be visually similar to the Posner task as described above and previously (Small et al., 2003). The reason for this was that we initially considered comparing sleep deprivation effects on attention networks with effects on frontal cognitive control networks. In order to do this properly, the testing environment needs to be as similar as possible for both conditions. In this way, I attempted to minimize sensory-motor processing differences that could confound the results, varying only the cognitive demands of the task.

Figure M.4 illustrates trial organization and timing. Participants were instructed to keep their eyes fixed on a diamond in the center of the screen throughout the experiment, and to respond alternately to the appearance of "X's" and "+'s" (targets) in peripheral boxes located 7° degrees to the left and right of fixation. Participants were specifically instructed to inhibit responding to the appearance of any other symbols (non-targets) and repeated target symbols (lures), e.g. an "X" following an "X" or a "+"

following a "+". Targets made up 53% of all trials, non-targets made up 29%, and lures made up 18%. Targets were termed a 'Go' stimulus, and non-targets and lures were termed 'No-go' stimuli. Onset of symbols was preceded by a non-directional cue that appeared at the point of fixation. To avoid generation of temporal expectancies we used different stimulus onset asynchronies (SOA) between cue and target appearance: 200, 400, and 800 ms. The intertrial interval varied as a function of these delays in order to maintain a trial length of 2.1 seconds. Target reaction times less than 100 ms or responses to inhibition events (non-targets and lures) were termed "errors", and target reaction times greater than 1000 ms or target trials with no response were considered "lapses".

An event-related design was used. Each experimental run contained 152 trials (81 targets, 44 nontargets, and 27 lures). Fifty null events were distributed throughout the run to allow deconvolution of the hemodynamic response function (HRF) (Burock et al., 1998). These events consisted of a passive display for 2.1-6.3 seconds. Each participant completed two fMRI runs of the task during the Sleep Opportunity (SO), Sleep Deprivation (Sd), and Sleep Recovery (SR) conditions. In order to train participants, all scripts were practiced in the GCRC before the second night of sleep recording in both visits. In order to build up response prepotency, an alternate version of the go/no-go task was completed. In this version, each run contained 152 trials (100 targets, 42 nontargets, and 10 lures).

Behavioral analysis

Behavioral data collected within the scanner for sleep opportunity, sleep deprivation, and sleep recovery conditions were analyzed for this report. For data collected in the scanner, comparisons between sleep opportunity and sleep deprivation are presented in chapter 2, and comparisons between sleep opportunity and sleep recovery are presented in chapter 3. Percent of correct inhibitions (the inverse of percent of errors of commission) and correct responses (the inverse of percent of errors of omission) were calculated for each subject in each condition. A correct inhibition was defined as a non-response to either a lure or a non-target. Target responses were defined as a response to a target trial with a reaction time (RT) $\leq$ 1000 ms. In addition, in order to examine the effects of age and sleep condition on the interaction of correct responses and correct inhibitions, the behavioral data were analyzed using signal detection theory which creates a metric, d', relating to response accuracy. This metric is derived from the proportions of correct responses, correct inhibitions, misses, and false alarms (Green & Swets, 1966). Two-way, repeated-measures ANOVAs were used to compare each percentage of correct inhibitions and target responses across age groups (Young, Old) and sleep state (SO, Sd, SR). Two-sample t-tests using a Bonferroni correction for multiple comparisons were used to identify performance differences between sleep states and age groups.

For data collected outside the scanner, percent of correct inhibitions, correct responses, d', target mean reaction time, and standard deviation of target reaction time are examined and presented in the Appendix. A three way, repeated measures ANOVA is used on time points repeated in all three conditions. In this analysis, condition (SO, Sd,

and SR) and time (8:30, 10:30, 12:30, and 14:30) are within subject factors, and age (young, old) is a between subjects factor. This analysis separates the effects of time of day from condition. For this analysis, since baseline measurements are taken during the baseline visit and at the beginning of the sleep deprivation visit, SO data are calculated as the average between values collected during the baseline visit and at the beginning of the sleep deprivation visit.

All behavioral data were analyzed using SPSS version 16.0 (SPSS, Inc., Chicago, IL), or Statistica 6.0 (StatSoft, Inc., Tulsa, OK).

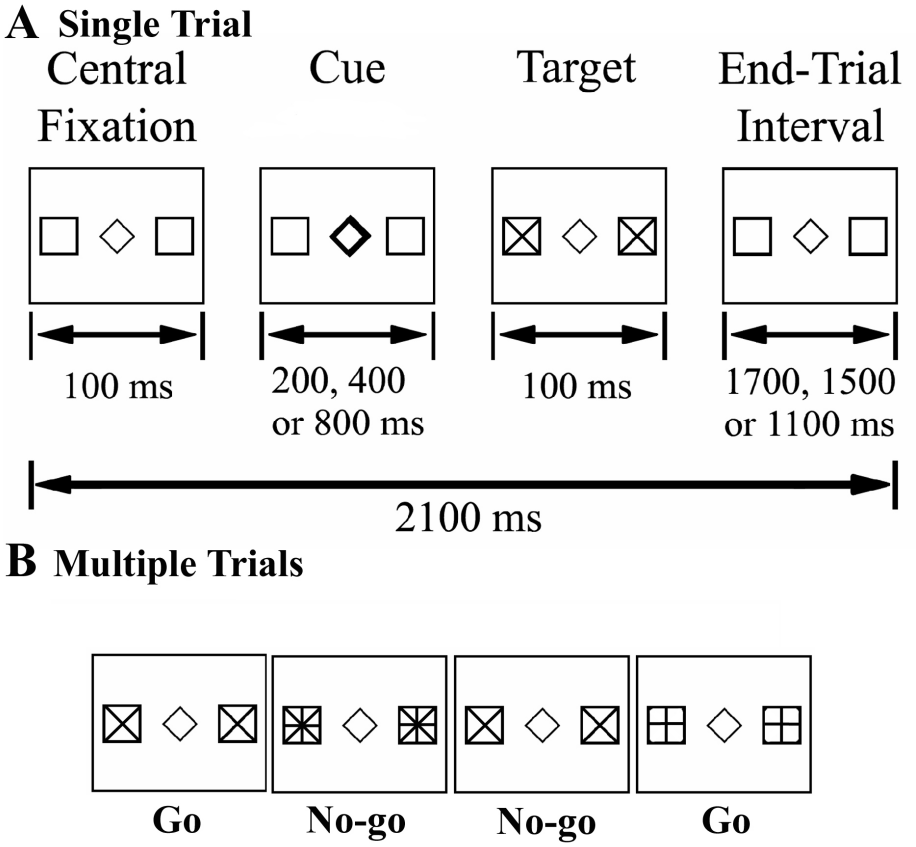

Figure M.4. Schematic representation of the Go/No-go task, and the timing and organizational parameters of a single trial (A) and multiple trials (B). Subjects performed two runs in the scanner in each session. An event-related design was used. A) Each trial consisted of fixation followed by a non-spatial cue presented for 200, 400, or 800 msecs. Following the cue, a stimulus was presented for 100 msecs. The intertrial interval varied as a function of the SOA length to maintain an overall trial length of 2100 msecs, matching TR length. B) An example of a series of four trials is presented. The correct response would be to respond to the first and last Go (target) stimuli, but to inhibit responding to the middle two No-go stimuli (non-target and lure, respectively).

Functional imaging methods

MRI scanning

Subjects were imaged using a Siemens Trio 3.0-T scanner equipped with a transmit and receive head coil. Both anatomical (T1) and functional scans were acquired. T_1-weighted anatomical images were obtained using a 3D MPRAGE protocol with the following parameters [repetition time/echo time (TR/TE) 2100 ms/4.38 ms, flip angle 8°, field of view (FOV) 220 mm, matrix 256 ×256, slice thickness 1.0 mm, 160 slices]. Anatomical scans were obtained in axial planes parallel to the anterior commissure-posterior commissure (AC—PC) line. Thirty-four contiguous 3-mm slices aligned to the AC-PC line (3×3×3 mm resolution) were acquired using a susceptibility-weighted single-shot EPI method in order to image the regional distribution of the BOLD signal (TR/TE 2100/30ms, flip angle 90°, FOV 220, 64×64 matrix). In all functional runs, the MR signal was allowed to reach equilibrium over the six initial scans, which were excluded from analysis.

In the scanner subjects viewed images that were projected onto a nonmagnetic screen located approximately 65 cm from their eyes. Head movement was reduced by using a vacuum pillow (VacFix, Toledo, OH) and a cloth collar (Scott Specialties, Inc., Belleville, KS). Subjects responded using a fiber-optically linked button.

VBM analysis

It is possible that age-related differences in the BOLD response are due to gray matter differences. In order to address this, voxel based morphometry (VBM) was used to determine differences in gray matter volume. Data and preprocessing was performed

using Christian Gaser's VBM 5.1 tool box (version 1.15; University of Jena, Department of Psychiatry; http://dbm.neuro.uni-jena.de/vbm/) within SPM5 running under a Matlab environment. Data preprocessing involved the following steps: 1) spatial normalization, 2) segmentation applying a Hidden Markov Random Field (HMRF) model which does not require the use of priors, 3) modulation, and 4) spatial smoothing with a Gaussian kernel. A two sample t-test was used to compare gray matter volume between the two age groups. Absolute threshold masking was used to restrict the analysis to gray matter changes. A liberal threshold (0.05) followed by more restrictive thresholds (0.1, 0.15, 0.2) were used.

fMRI analysis

Data analysis of all fMRI data were conducted using the Statistical Parametric Mapping version 5 (SPM5) software packages (Wellcome Department of Imaging Neuroscience http://www.fil.ion.ucl.ac.uk/spm) running in the Matlab environment (Mathworks, Inc., Sherborn, MA). Analyses for each chapter will be described separately, as they involved specific procedures.

Chapter 2: Age alters the neural response to sleep deprivation within frontal cortex

Functional data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) running under a Matlab environment (Mathworks, Inc., Sherborn, MA). Functional images were slice timing corrected, realigned and then coregistered to the anatomic T1 volume. The T1 volume was then

normalized to the MNI-305 template supplied with SPM5. The template approximates the space described in the atlas of Talairach and Tournoux (Tailairach & Tournoux, 1988).

At the individual subject level, neural responses to correct inhibitions, errors of commission (errors), correct responses (targets), and errors of omission (lapses) were examined. BOLD responses to lures and non-targets were compared in the SO and Sd conditions in all subjects. Since the neural response to lures and non-targets did not differ significantly, they were combined as inhibitory events, in subsequent contrasts. Affine movement parameters were included in the design matrix to model residual movement-related effects. Within each scanning session, subjects were run on the task twice using different trial orders. The conditions for each run were modeled separately in the design matrix. The fMRI design matrix did not include a global covariate, as it can bias the parameter estimates (Aguirre et al., 1998). Instead, a voxel-level linear model of the global signal (LMGS), which has been shown not to introduce bias, was used to remove global effects (Macey et al., 2004). Additionally, the small number of commission errors made by each individual may have impacted the reliability of error-related activations. However, subjects averaged between twenty to thirty events per sleep condition. A study by Murphy and colleagues demonstrated that minimal differences were present even between 25 and 150 trial events in terms of activation extent and reliability of activation (Murphy & Garavan, 2005).

Group activations were assessed by a second level random effects analysis, using a full factorial model with sleep condition (sleep opportunity, sleep deprivation; assuming unequal variance) and response type (correct inhibitions, errors, targets, lapses; assuming

unequal variance) as within subject factors and age (young, old; assuming unequal variance) as a between subjects factor. All parameter effect images for each response type within each sleep condition and within each age group were forwarded to this second level analysis. In order to isolate BOLD responses that related more specifically to response inhibition, motor output, error processing, and response selection the following t-contrasts were examined. BOLD responses in all these contrasts were compared across sleep conditions and age groups to examine age, sleep condition and age by sleep condition group effects. Data are presented in tables 2.1-2.5. Table 2.1 presents the significant age by sleep condition interactions for all contrasts. Tables 2.2-2.5 show main effects of task, age, and sleep condition for each contrast. When denoted SO or Sd, activations are presented as significant effects present in the SO or Sd condition. When denoted SO-Sd, activations are significantly greater in the SO than Sd condition. The opposite is true for the Sd-SO denotation.

Response inhibition: *Responses to correct inhibitions were compared to responses to targets (correct inhibitions – targets contrast).* This contrast was chosen to examine activity primarily related to inhibitory control by attempting to discount effects of attention, maintenance of information within working memory, and motor planning. We have used a similar contrast previously (Booth et al., 2003), and this contrast has been used by others on comparable tasks (Laurens, Kiehl, & Liddle, 2005; Menon, Adleman, White, Glover, & Reiss, 2001).

Motor output (inverse of response inhibition contrast): *Responses to targets were compared to responses to correct inhibitions (targets – correct inhibitions contrast).* This contrast was chosen to examine activity primarily related to motor output by attempting to discount the effects of response selection, attention, and working memory (Laurens et al., 2005).

Error processing: *Responses during commission errors were compared to responses to targets (errors – targets contrast).* Other reports have examined errors alone, or errors in comparison with inhibition trials (Garavan et al., 2002; Menon et al., 2001). It is likely that motor-related activity is present during error events. This is particularly important given the importance of dorsal anterior cingulate cortex for error processing, an area associated with the coordination of motor actions (Wenderoth, Debaere, Sunaert, & Swinnen, 2005). Thus, this contrast was chosen to examine activity primarily related to error processing by attempting to discount effects of attention, maintenance of information within working memory, motor planning, and motor output.

Response selection (inverse of error processing contrast): *Responses to targets were compared to responses to errors (targets – errors contrast).* This contrast was chosen to examine activity primarily related to response selection by attempting to discount effects of attention, maintenance of information within working memory and motor components. We expect this contrast to isolate processes associated with decisions to act that have been correctly selected from within working memory (Heekeren, Marrett, Bandettini, &

Ungerleider, 2004; Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). Under the current experimental paradigm, a prepotency to respond has been built up. Thus, errors should be primarily due to a failure to select responses based on context. Target responses, however, should primarily depend on the prefrontal adaptation of behavior to the appropriate context. Thus, the relative difference between these events should reflect a greater reliance on the prefrontal-dependent selection of responses within the relevant context.

Whole brain analysis

In order to examine the interacting effects of sleep deprivation and age on whole brain function associated with response inhibition, motor output, error processing, and response selection abilities, a whole brain analysis was conducted as well. Group activations were searched for at a mapwise threshold of $p = 0.001$ uncorrected. Regions were considered significant at a cluster level of $p < 0.05$ corrected for multiple comparisons across the entire brain volume. All data presented in the current report are presented in MNI coordinates.

ROI Analysis

Since prefrontal cortex is considered to be affected by age and sleep deprivation, we would expect that the interaction of age and sleep deprivation would cause differential changes within prefrontal cortex. Further, since right prefrontal functioning is particularly linked to inhibitory control we would expect age by sleep deprivation

interactions to be located within right prefrontal cortex. Since these changes were not clearly observed in the whole brain analysis, we explored the right prefrontal cortex more closely to determine if more subtle age by sleep debt interactions could be detected within the right prefrontal cortex. Regions within the right prefrontal cortex associated with response inhibition were pre-identified for a region of interest analysis using MarsBaR volume of interest (VOI) analysis toolbox within SPM5 (Brett, Anton, Valabregue, & Poline, 2002). Mean contrast estimates within three clusters were extracted with the following coordinates as their maxima: VOI-1 = [x= 45, y=6, z=27, 137 voxels (young adults)]; VOI-2: = [x=36, y=21, z=6, 349 voxels (young adults)]; VOI-3: = [x=39, y=36, z=27, 68 voxels (old adults)]. Mean values were compared across age and sleep condition. These regions were chosen, because they showed activation during the 'response inhibition contrast' (correct inhibitions – targets contrast) in the baseline SO condition and neural responses within these regions have been associated with inhibitory control in other studies (VOI-1 (Bellgrove et al., 2004; Booth et al., 2003; Garavan et al., 2002; Laurens et al., 2005; Rubia et al., 2001), VOI-2 (Bellgrove et al., 2004; de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Garavan et al., 1999; R. L. Hester et al., 2004; Horn et al., 2003; Konishi et al., 1999; Matthews et al., 2005; Menon et al., 2001; Nielson et al., 2002; Rubia, Smith, Brammer, & Taylor, 2003; Watanabe et al., 2002), VOI-3 (Bellgrove et al., 2004; de Zubicaray et al., 2000; Garavan et al., 2002; Garavan et al., 1999; R. L. Hester et al., 2004; Matthews et al., 2005; Rubia et al., 2001; Watanabe et al., 2002)). These data were analyzed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

To explore the nature of increased left prefrontal activation observed in young adults further (see chapter 2 results), activation in this cluster was extracted using MarsBaR as well [x= -30, y= 15, z= 39, 167 voxels]. Performance variables (percent correct responses, percent correct inhibitions, dprime) were then correlated with mean contrast estimates to determine whether this activation was compensatory or not. Spearman's rho was used for this calculation. This analysis was conducted with SPSS version 16.0 (SPSS, Inc., Chicago, IL).

Chapter 3: Age alters neural responses associated with recovery from sleep deprivation within the prefrontal cortex

Functional data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) running under a Matlab environment (Mathworks, Inc., Sherborn, MA). Functional images were slice timing corrected, realigned and then coregistered to the anatomic T1 volume. The T1 volume was then normalized to the MNI-305 template supplied with SPM5. The template approximates the space described in the atlas of Talairach and Tournoux.

At the individual subject level, neural responses to correct inhibitions, errors of commission (errors), and correct responses (targets) were examined. Affine movement covariates were also included in the design matrix to model residual movement-related effects. Within each scanning session, subjects completed two versions of the task and underwent scanning twice. A covariate was included to control for effects of task version. SO and SR runs were modeled as separate sessions. The fMRI design matrix

did not include a global covariate, as it can bias the parameter estimates (Aguirre et al., 1998). Instead, a voxel-level linear model of the global signal (LMGS), which has been shown not to introduce bias, was used to remove the global effects (Macey et al., 2004).

Group activations were assessed by a second level random effects analysis, using a full factorial model with sleep condition (sleep opportunity, sleep recovery) and response type (correct inhibitions, commission errors, targets) as within subject factors and age (young, old) as a between subjects factor.

Regions within the right and left prefrontal cortex were pre-identified for a region of interest analysis using MarsBaR volume of interest (VOI) analysis toolbox within SPM5 (Brett et al., 2002). These regions were chosen, because neural responses within these regions are altered by sleep deprivation while performing this task (see chapter 2 entitled 'alters the neural response to sleep deprivation within frontal cortex'), and these regions are recruited by inhibitory tasks (Bellgrove et al., 2004; Booth et al., 2003; Garavan et al., 2002; Rubia et al., 2001; Watanabe et al., 2002). Mean contrast estimates were extracted from each right prefrontal cluster described in chapter 2: VOI-1 = [x= 45, y=6, z=27, 137 voxels (young adults)]; VOI-2: = [x=36, y=21, z=6, 349 voxels (young adults)]; VOI-3: = [x=39, y=36, z=27, 68 voxels (old adults)]. Additionally, mean contrast estimates were extracted from the left prefrontal cluster observed to be increased following sleep deprivation in young adults: [x= -30, y= 15, z= 39, 167 voxels].

Responses to correct inhibitions were compared to responses to targets (correct inhibitions – targets contrast). This contrast was chosen to examine activity primarily related to inhibitory control by attempting to discount effects of attention, maintenance of

information within working memory, and motor planning. We have used a similar contrast previously (see section on chapter 2 above, (Booth et al., 2003)), and this contrast has been used by others (Laurens et al., 2005; Menon et al., 2001). These contrasts were compared across sleep conditions and age groups. In order to examine the relationship between activation and inhibitory performance after sleep recovery, change in activity from SO to SR conditions was regressed against change in inhibitory performance from SO to SR conditions in both young and old adults. Regression analysis was completed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

In order to examine relationships between spectral EEG variables and brain activity during inhibitions measures of absolute delta and sigma power (the spectra for slow waves and spindles, respectively) were regressed against activation associated inhibitions (correct inhibitions – targets contrast). Mean delta power over the first three hours of the sleep period were calculated for both the averaged baseline night data (See section 'PSG recording and analysis' for details) and recovery night data. Following sleep deprivation, the most prominent increase in delta power occurs in the first three hours of the night (Borbely et al., 1981). One can hypothesize that this increase in delta in the early hours of the sleep period plays a dominant role in the dissipation of the sleep drive. This measure of delta power was compared across condition to determine the increase in delta power from baseline to recovery. This is reported as percent change in delta power from baseline to recovery conditions. This measure of change in early delta from baseline to recovery was then regressed against the change in BOLD signal from SO to SR during inhibitions (correct inhibitions – targets contrast). A similar method

was used for comparisons between sigma power and brain activation. Sigma power increases across the night due to slow wave suppression of spindle activity which lessens as slow wave activity decreases across the night (Dijk, Hayes, & Czeisler, 1993). Since this is the case, mean sigma power over the last three hours of the sleep period were compared across conditions. This is reported as percent change in delta power from baseline to recovery conditions. This measure of change in late sigma from baseline to recovery was then regressed against the change in BOLD signal from SO to SR during inhibitions (correct inhibitions – targets contrast). Finally, changes in delta and sigma power were regressed against changes in inhibitory performance. Regression analysis was completed using SPSS version 16.0 (SPSS, Inc., Chicago, IL).

Chapter 4: Associations between baseline brain activation and the behavioral response to sleep loss and recovery in young and old adults.

Functional data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm) running under a Matlab environment (Mathworks, Inc., Sherborn, MA). Preprocessing steps and fMRI analyses at the individual level are as described above in sections 'Chapter 2: Age alters the neural response to sleep deprivation within frontal cortex' and 'Chapter 3: Age alters neural responses associated with recovery from sleep deprivation within the prefrontal cortex'.

Associations between baseline brain activation and performance change after sleep deprivation and recovery were assessed using multiple regression models. Inhibitory performance change between Sleep deprivation (Sd) and Sleep Recovery (SR)

conditions and the Sleep Opportunity (SO) condition were included as regressors in separate models including SO correct inhibition (No-go) and target (Go) events. The change in percent of correct inhibitions was used as a metric of inhibitory ability, and was regressed against the BOLD response during SO correct inhibitions. The change in percent of correct responses was used as a metric of response selection ability, and was regressed the BOLD response during SO target events. Comparisons between SO and Sd and SO and SR were conducted separately. In summary, the following comparisons were conducted: 1) SO-Sd change in percent correct inhibitions versus SO activation during correct inhibition events; 2) SO-SR change in percent correct inhibitions versus SO activation during correct inhibition events; 3) SO-Sd change in percent correct responses versus SO activation during target events; 4) SO-SR change in percent correct responses versus SO activation during target events. These analyses were conducted separately in young and old adults.

It is important to note that performance change was the predictor variable. Thus, brain activity cannot predict performance change, but is merely associated with performance change. Future studies can utilize these data to isolate regions of interest to determine if activation in specific brain areas can predict performance change after sleep deprivation across individuals.

In addition, changes in activation from SO to Sd and SO to SR were regressed against performance change, in order to examine brain-performance relationships. These were also conducted using multiple regression, and were conducted separately for change in percent correct inhibitions and correct responses. In summary, the following

comparisons were conducted: 1) SO-Sd change in percent correct inhibitions versus SO-Sd activation during correct inhibition events; 2) SO-SR change in percent correct inhibitions versus SO-SR activation during correct inhibition events; 3) SO-Sd change in percent correct responses versus SO-Sd activation during target events; 4) SO-SR change in percent correct responses versus SO-SR activation during target events. These analyses were conducted separately in young and old adults.

Activations in all the above analyses were searched for at a mapwise threshold of $p = 0.001$ uncorrected. Regions were considered significant at a cluster level of $p < 0.05$ corrected for multiple comparisons across the entire brain volume.

Chapter 1: Sleep deprivation alters functioning within the neural network underlying the covert orienting of attention*

*These data are published in a report in Brain Research (Mander, B.A., et al, Brain Res 2008, 1217:148-56.)

Abstract

One function of spatial attention is to enable goal-directed interactions with the environment through the allocation of neural resources to motivationally relevant parts of space. Studies have shown that responses are enhanced when spatial attention is predictively biased towards locations where significant events are expected to occur. Previous studies suggest that the ability to bias attention predictively is related to posterior cingulate cortex (PCC) activation (Small et al., 2003). Sleep deprivation (Sd) impairs selective attention and reduces PCC activity (Strangman, Thompson, Strauss, Marshburn, & Sutton, 2005; Thomas et al., 2000). Based on these findings, we hypothesized that Sd would affect PCC function and alter the ability to predictively allocate spatial attention. Seven healthy, young adults underwent functional magnetic resonance imaging (fMRI) following normal rest and 34-36 hours of Sd while performing a task in which attention was shifted in response to peripheral targets preceded by spatially informative (valid), misleading (invalid), or uninformative (neutral) cues. Subjects responded more quickly to validly than neutrally and invalidly cued targets when rested, but not when sleep-deprived. Brain activity during validly cued trials with a

reaction time benefit was compared to activity in trials with no benefit. PCC activation was greater during trials with a reaction time benefit following normal rest. In contrast, following Sd, reaction time benefits were associated with activation in the left intraparietal sulcus, a region associated with receptivity to stimuli at unexpected locations. These changes may render sleep-deprived individuals less able to anticipate the locations of upcoming events, and more susceptible to distraction by stimuli at irrelevant locations.

Introduction

Sleep loss is common among the adult population. Only 26% of adults report getting the recommended 8 or more hours of sleep per night, and fifty percent of adults report feeling so sleepy that it interferes with their daily activities at least 1-2 times per week (National Sleep Foundation, 2005). Behavioral studies have demonstrated that sleep loss adversely affects a number of neurobehavioral domains, and in some cases this impairment is as great as that observed in individuals who are intoxicated (Dawson & Reid, 1997; D. Dinges & Kribbs, 1991).

Deficits in attention appear to underlie many of the performance impairments associated with sleep deprivation (D. Dinges & Kribbs, 1991). Sleep-deprived individuals are impaired in both shifting attention towards relevant stimuli (Gunter et al., 1987; Norton, 1970) and ignoring irrelevant or potentially misleading information (McCarthy & Waters, 1997; Norton, 1970).

One physiological correlate of attentional responses is the electrodermal orienting response to auditory stimuli. Following sleep deprivation, it is delayed, shows reduced amplitude, and habituates faster (McCarthy & Waters, 1997). These findings have been taken to indicate that sleep deprivation results in slower shifts to novel stimuli, decreased attentional allocation to stimuli, and a more rapid loss of attention to repeated stimuli, respectively. In addition, event related potentials during a cueing task in sleep-deprived subjects showed delayed latency at P255 and N350 at Cz and P3b at Pz, suggesting delayed covert orienting (Gunter et al., 1987). These studies support the notion that sleep loss impairs the effective allocation of attention to relevant target stimuli.

In a previous functional magnetic resonance imaging (fMRI) study, activity in the posterior cingulate cortex (PCC) was related to the speed of response to spatially cued targets (Mesulam et al., 2001). Small et al. (2003) subsequently demonstrated that PCC activity was more specifically related to the degree that attention can be allocated, predictively (Small et al., 2003). This study calculated cue benefits as a metric of anticipatory attentional biasing. Cue benefits were defined as the reduction in response speed (i.e., faster responses) to targets preceded by directionally informative versus directionally uninformative cues. Greater cue benefits were associated with both faster reaction times to the spatially informative cues, consistent with the anticipatory biasing of spatial attention, and increased PCC activity (Mesulam et al., 2001; Small et al., 2003). In contrast, as cue benefits disappeared, intraparietal sulcus (IPS) activation was increased. This suggests that predictive attentional biasing was reduced on these trials,

and that subjects were instead using a more global spatial strategy, potentially increasing their susceptibility to distracting stimuli.

Previous functional imaging studies have demonstrated reduced resting cerebral metabolism in posterior cingulate cortex both during sleep (Vogt & Laureys, 2005) and following sleep deprivation (Thomas et al., 2000). Furthermore, left parietal but not PCC activation was seen when subjects performed tasks following sleep deprivation versus a normal night of sleep (Strangman et al., 2005). These studies indicate that PCC activity is reduced by sleep deprivation. Based on our previous studies showing an association of PCC activity with predictive attentional orienting, we hypothesized that sleep loss would affect this relationship, leading to reduced PCC activity and an impaired ability to expectantly bias attention.

Results

Behavioral Data

In order to examine the effects of sleep deprivation on the relationship between PCC activity and attentional orienting, seven subjects underwent fMRI scanning while performing a Posner-type task of attentional orienting (see methods) in sleep opportunity (SO) and sleep-deprived (Sd) conditions. While performing the task, subjects fixated centrally and were presented a series of peripheral target and foil symbols preceded by informative (valid), misleading (invalid), or uninformative (neutral) cues. To avoid the generation of temporal expectancy, cue-target stimulus onset asynchronies (SOA) were 200, 400, or 800 ms. Behavioral measures of errors of omission and commission, and

mean reaction times for each trial type (valid, invalid, and neutral) with errors removed were calculated (see methods). Additionally, valid trials were separated into valid trials conferring a cue benefit on reaction time and valid trials that did not confer a cue benefit (V^+ and V^- respectively, see methods). These behavioral metrics were used to examine the effects of sleep deprivation on sustained attention and attentional orienting.

Performance was impaired in subjects following 34-36 hours of sleep deprivation as opposed to when they had a full night of sleep. Following Sleep deprivation, subjects made more errors of omission (SO: 1.48% ± 0.41% *vs* Sd: 24.35% ± 4.93%, p = 0.004) but showed no difference in commission errors (SO: 3.88% ± 0.43% *vs* Sd: 4.64% ± 0.51%, p = 0.28) compared with following a normal night of sleep. There were no differences in omission or commission errors by trial type (invalid, neutral, valid), side of target or SOA.

A two way ANOVA revealed significant differences in reaction times across cue types ($F_{2,12} = 14.27$, $p < 0.001$), but not between sleep states ($F_{1,6} = 0.068$, $p > 0.8$), see Table 1.1. There was a significant Sleep State by Cue Type interaction ($F_{2,12} = 6.15$, $p = 0.014$). All other main effects (side of target, SOA) and interactions were not significant. Bonferroni *post hoc* testing revealed no significant difference between sleep states for any cue type (valid p = 0.15; neutral p = 0.07; invalid p = 0.466). Within sleep state *post hoc* testing using the Games-Howell correction for repeated measures revealed that valid trials were faster than both neutral and invalid trials ($p < 0.001$ for valid versus neutral; $p = 0.024$ for valid versus invalid) when subjects were rested, but not after 34-36 hours of sleep deprivation ($p = 0.109$ for valid versus neutral; $p = 0.207$ for valid versus invalid);

invalids were also faster than neutral trials for rested but not sleep deprived subjects ($p = 0.031$ for rested; $p = 0.982$ for sleep-deprived) . Sleep-deprived subjects had significantly fewer valid trials showing a cue benefit (SO: 66.0% ± 5.99% vs. Sd: 46.4% ± 8.24%, $p = 0.003$). Of note, there was no significant difference between sleep states in the means or variances of the distribution of reaction times (see table 1.1). Within subject variance for neutral trials was not different across sleep states (Rested 8.0±1.4 ms; Sleep-deprived 10.7±3.4 ms, $t_{paired} = -1.91$, $p > 0.1$). This is important, since neutral trials were used to categorize valid trials.

Table 1.1: Behavioral Results

	Mean RT (SE) by Sleep State (msecs)	
	Sleep Opportunity	Sleep-deprived
Valid	272 (2.7)	281 (3.0)
Neutral	301 (3.3)	292 (3.6)
Invalid	285 (5.3)	293 (6.1)

fMRI Data

As in our previous studies, blood oxygen level dependent (BOLD) responses during valid trials (i.e., trials with valid cues) were analyzed (Gitelman et al., 1999; Mesulam et al., 2001; Small et al., 2003). Specifically, BOLD responses were examined for contrasts between V^+ and V^- trials in Sd and SO states. Contrasting these events allows for the examination of the effects of sleep deprivation on neural mechanisms relevant to attentional orienting. During data collection, functional data was lost in one subject leaving six subjects for all fMRI analyses.

Simple main effects relating to the presence of cue benefit (V^+ - V^-) in the rested state showed greater activation within the PCC, Table 1.2. The "positive" interaction of sleep state (SO - Sd) with cue benefit ($V^+ - V^-$) showed significantly greater BOLD responses within the posterior cingulate and the bilateral middle-temporal gyri (mTG), Table 1.2 and Figure 1.1A. In contrast, the "negative" interaction of sleep state (Sd – SO) with cue benefit ($V^+ - V^-$) demonstrated greater activation within the medial intraparietal sulcus, Table 1.2 and Figure 1.1B.

In order to examine the interaction effects more closely, BOLD signal was extracted for both sleep states from the maxima in the PCC (xyz: -6 -57 21) and IPS (xyz: -12 -69 51) clusters, and plotted as peri-stimulus time histograms, Figure 1.2. In the rested state, activity in the PCC was increased for V^+ trials and reduced for V^- trials. Following Sd, activity in the PCC did not change significantly for either V^+ or V^- trials.

In contrast, in the Sd state IPS activity was increased during V^+ trials and reduced during V^- trials.

The $V^- - V^+$ contrast was also examined to determine areas that were more active in the absence of a cue benefit. In the rested state, activations were seen in right inferior parietal cortex, while in the Sd state, activations were seen in the right middle temporal gyrus and left inferior frontal gyrus.

In SPM the calculation for cluster statistics is dependent on the "smoothness" of the region, i.e. the average number of voxels containing BOLD signals that significantly correlate with each other (Hayasaka et al., 2004). Under lower degrees of freedom, this value is more likely to vary across the image. Regions that are "smoother" have a greater chance of containing false positive clusters. In order to reduce the chance of a Type I error, a measure of smoothness, full width at half maximum (FWHM), was examined. Clusters with a mean FWHM larger than the one used by SPM, were designated as non-significant because of the greater chance of a false positive cluster in these regions. The mean FWHM for each cluster is listed in Table 1.2. The FWHM values used by SPM for each of the contrasts are in parentheses. As shown in Table 1.2, the actual FWHM of the clusters was smaller than the FWHM used by SPM, suggesting no increase in Type I error for these clusters.

Table 1.2: Activations by sleep state and contrast

Sleep State (Contrast) Brain Region	**MNI coordinates** x	y	z	**Z score**	**# of voxels**	**Mean (SPM) and cluster FWHM mm**
SO ($V^+ > V^-$)						(9.10)
Posterior cingulate cortex	0	-39	45	3.83	12	7.30
SO ($V^- > V^+$)						(9.37)
Right inferior parietal lobule	30	-63	33	4.09	35	7.12
Right inferior parietal lobule	36	-75	27	3.78	18	5.66
Sd ($V^- > V^+$)						(9.37)
Right middle temporal gyrus	51	-57	0	4.10	29	7.49
Left inferior frontal gyrus	-57	12	24	3.88	13	6.10
SO - Sd ($V^+ > V^-$)						(9.37)
Left posterior cingulate cortex	-6	-57	21	3.72	14	7.96
Left middle temporal gyrus	-54	-9	-24	4.41	61	7.25
Right middle temporal gyrus	63	-6	-15	4.03	17	7.37
SO – Sd ($V^+ > V^-$)						(9.37)
Left intraparietal sulcus	-12	-69	51	4.06	26	6.15

All clusters were significant at $p < 0.05$ after correction for multiple comparisons.

Figure 1.1

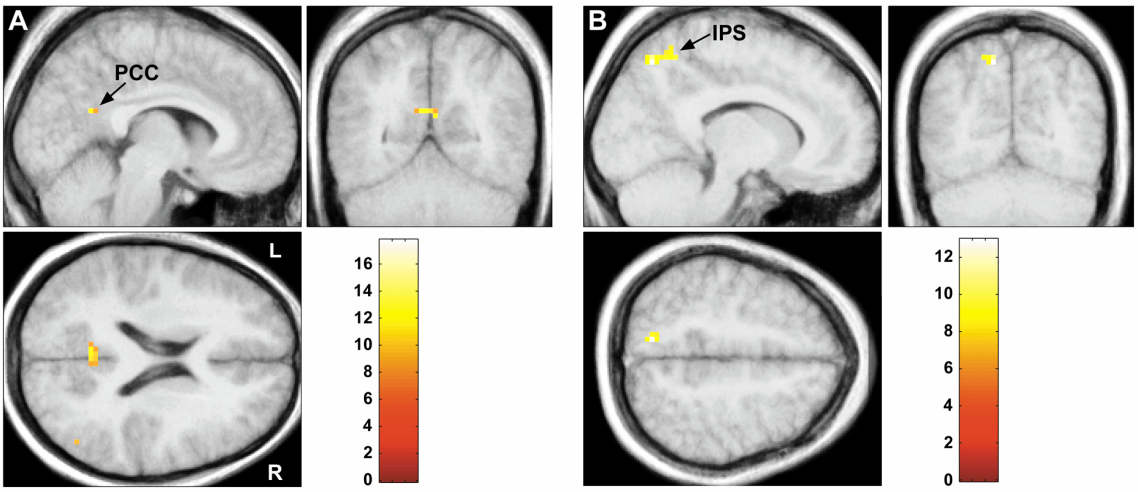

Figure 1.1. Activation related to the presence of cue benefit ($V^{+} - V^{-}$). A) PCC activation in the sleep opportunity state greater than the sleep-deprived state. B) IPS activation in the sleep-deprived state greater than the sleep opportunity state. All peaks are significant at $p < 0.05$ corrected at the cluster level. The color bar identifies the t-values.

Figure 1.2

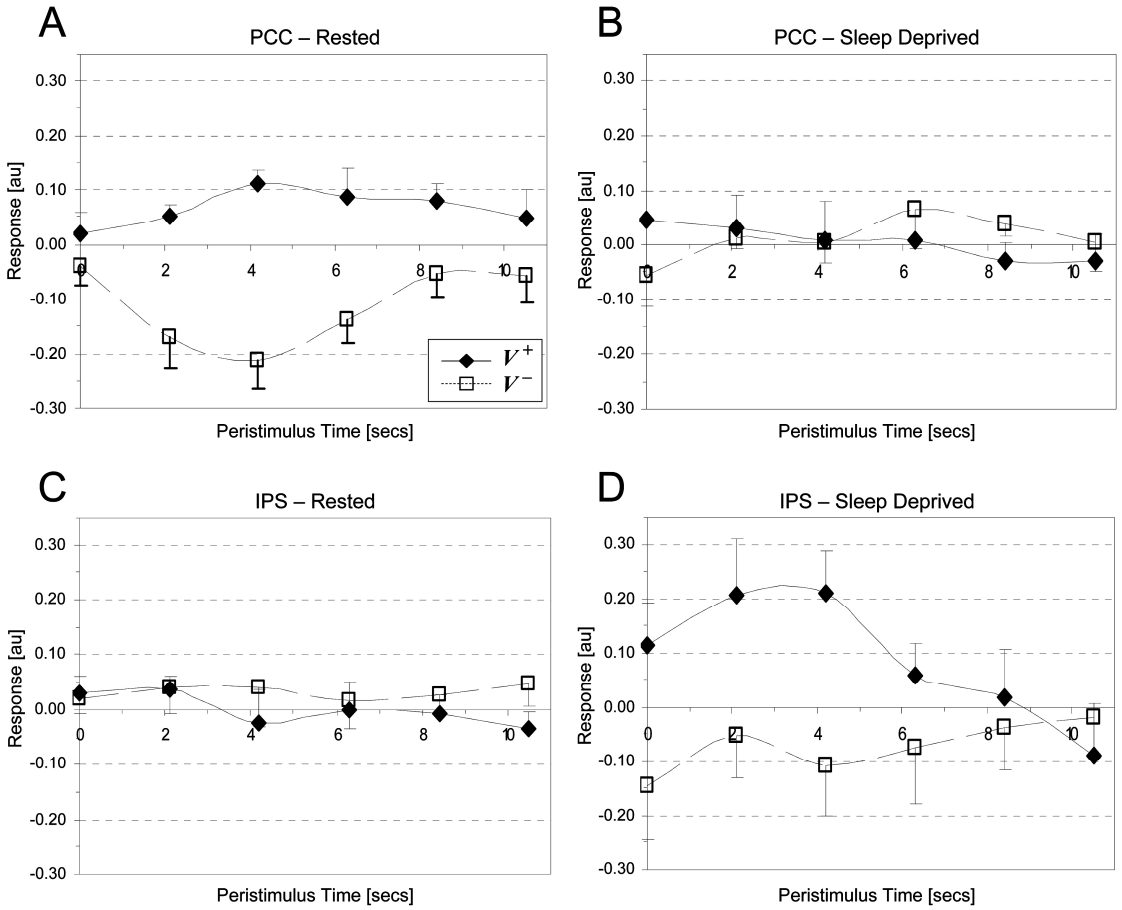

Figure 1.2. Peri-stimulus time histograms for V^+ (diamonds) and V^- (squares) trials in Rested (SO) and Sleep Deprived states for the maxima from the PCC (xyz: -6 -57 21) and IPS (xyz: -12 -69 51) clusters. (A) Mean group BOLD responses in the rested state within the PCC for V^+ (solid line) and V^- (dashed line) trials. (B) Mean group BOLD response in the sleep-deprived state within the PCC for V^+ and V^- trials. (C) Mean group BOLD response in the rested state within the IPS for V^+ and V^- trials. (D) Mean group BOLD response in the sleep-deprived state within the IPS for V^+ and V^- trials.

Values are group means ± standard error of the mean. The graphs demonstrate the greatest cue benefits (difference between V^+ and V^-) in the PCC when subjects are rested (3A) and the IPS when they are sleep deprived (3D).

Discussion

This preliminary report examined the influence of sleep state on the neural mechanisms underlying the anticipatory biasing of spatial attention. Previous reports have shown that sleep deprivation impairs performance and alters brain activity when subjects perform tasks targeting attention, verbal learning, and working memory (Chee & Choo, 2004; Drummond et al., 2000; Drummond et al., 2001; Thomas et al., 2000; Wu et al., 1991). The current results suggest that sleep deprivation may also impair the anticipatory allocation of attention in response to spatially predictive cues and alter the underlying neural correlates.

Following sleep deprivation, subjects performed less accurately and made significantly more errors of omission than when rested, which has been seen in other studies of sleep deprivation (Williams et al., 1959). Although there was no main effect of sleep state on reaction time, an interaction with the type of cue did affect subjects' responses such that valid trials were significantly faster than both neutral and invalid trials when subjects were rested but not when they were sleep-deprived. Sleep-deprived subjects also had significantly fewer trials conferring a cue benefit, despite the lack of differences in mean and variance of reaction times when cue types were compared individually between sleep states. These results suggest that sleep deprivation may lead to impairment in the anticipatory allocation of spatial attention through interacting effects on both spatial and non-spatial attentional components (de Gonzaga Gawryszewski,

Riggio, Rizzolatti, & Umilta, 1987; Jongen, Smulders, & van Breukelen, 2006; Mesulam et al., 2001; Small et al., 2003).

In the sleep opportunity state, the presence of a cue benefit was associated with activity within the PCC, whereas following sleep deprivation cue benefits were associated with activity within the IPS. Previous reports have also shown increased PCC activity when attention is shifted in response to spatially predictive cues (Hopfinger et al., 2001; Mesulam et al., 2001; Small et al., 2003). This relationship between performance and brain activity was demonstrated to be independent of reaction time, per se (Small et al., 2003). Instead, it was suggested that PCC activity was associated with the generation of a motivational bias for attending to a focal location in space (Small et al., 2003).

In contrast, studies have shown that IPS activity may display the opposite relationship to spatial cues, by demonstrating decreased activity when attention is allocated predictively to a location in space (Constantinidis & Steinmetz, 2001; Robinson, Bowman, & Kertzman, 1995; Small et al., 2003). These data have been taken to suggest IPS suppression may be necessary in order limit attentional receptivity to stimuli at unexpected locations. Consistent with these reports, the current study showed no change in IPS activity to spatial cues when subjects were rested, Figure 3C. However, in the SD state, IPS activity was increased for trials showing a cue benefit. Thus, when sleep-deprived, subjects appear to preferentially recruit the IPS when spatially orienting attention.

It is unclear why the relationship between cue benefit and brain activation is altered by sleep deprivation. One possibility is that PCC recruitment is impaired by sleep

deprivation. This notion is supported by studies demonstrating reduced activity within the PCC following Sd as compared to the sleep opportunity state when subjects performed serial addition/subtraction and complex navigation tasks (Strangman et al., 2005; Thomas et al., 2000). Furthermore, positron emission tomography (PET) imaging of wake and non-rapid eye movement sleep (NREM) states have shown that activity in posterior cingulate is significantly reduced in NREM sleep, while medial parietal regions remain as active as when awake (Nofzinger et al., 2002). It is often argued that in a sleep-deprived state, errors of omission predominantly represent a brief transition to NREM sleep (D. Dinges & Kribbs, 1991; Williams et al., 1959). Taken together, these data suggest that it is possible that PCC recruitment is impaired in the sleep-deprived state due to the intermittent suppression of PCC activity during errors of omission.

Because the recruitment of the PCC in the sleep-deprived state is impaired, the generation of cue benefit may depend on a strategy other than generating a motivational bias for attending to a focal location in space. We have shown that this strategy is associated with IPS activity. Greater IPS activity in the sleep-deprived state may reflect a strategy that relies on increasing receptivity to stimuli at unexpected locations. Thus, sleep-deprived individuals may shift from a focal endogenous orienting strategy to a global exogenous orienting strategy.

Another possibility is that sleep-deprived subjects rely more on eye-movements to perform the task than when rested. As we did not monitor eye movements in the present experiment, it is unclear whether or not this is the case. However, if this was the case we would expect to see greater activity in the frontal eye fields and lateral IPS, which was

not found (Corbetta et al., 1998; Nobre, Gitelman, Dias, & Mesulam, 2000). Another way to address that these activations are linked to actual cue benefit is by associating a parametric measure of cue benefit with brain activation. Cue benefit scores (CBS) were calculated as previously described and regressed against BOLD responses (Small et al., 2003). Results were similar further supporting that PCC and IPS activations were associated with cue benefit (see Table S1.1).

One limitation of the current study is the small number of subjects, which may potentially affect both the generalizability of the findings and the assumptions underlying the parametric statistics used to analyze the fMRI data. Random effects statistics were used to address the issue of population inference, and activations were found in the PCC and IPS. Similar sites of activation were also seen previously in other studies examining the anticipatory allocation of spatial attention (Mesulam et al., 2001; Small et al., 2003).

In order to address our use of cluster level parametric statistics in the setting of low degrees of freedom, we also calculated the mean FWHM values for each of the clusters, and compared these values with the average value used by SPM. In all cases, the FWHM in the cluster was smaller than the value used by SPM, suggesting that clusters identified as significant were unlikely to be false positives.

In the setting of low degrees of freedom, non-parametric statistics could have been used to analyze the fMRI data (Hayasaka et al., 2004). However, the power of this technique may also be reduced by the small number of subjects (n=6), which would have only allowed a limited number of resamplings ($2^6 = 64$). The constrained number of resamplings limits the lowest possible p-value to 1/64 = 0.0156, thereby reducing the

power of the technique (S. Hayasaka, personal communication). In the face of limitations to both parametric and non-parametric techniques, we chose to utilize standard parametric statistics, while attempting to minimize the chance of a Type I error. Nevertheless, replication and extension of these findings in a larger study will be important.

The standard reaction time pattern (Valid RT < Neutral RT < Invalid RT) was not replicated in the rested condition. Instead, neutral RT was slower than both valid and invalid trials. This has been reported in other central cueing studies, and has been attributed to reduced transient arousal in the absence of a spatially 'alerting' cue (Amir, Elias, Klumpp, & Przeworski, 2003; Perchet, Revol, Fourneret, Mauguiere, & Garcia-Larrea, 2001; Posner, Inhoff, & Friedrich, 1987). It is additionally possible that the neutral trials were not really 'neutral'. In order to address this concern, valid trials were separated using invalid trial reaction times (minus one SE). Results were similar (see Table S1.2), thus we are confident that the current analysis represents an effect of sleep deprivation on the anticipatory spatial biasing of attention.

In conclusion, sleep deprivation impairs the ability to utilize a predictive cue to shift attention towards relevant locations in space. This impairment is reflected in a lack of PCC activation, which has been implicated in the generation of an anticipatory bias for target location. Instead, it appears that SD subjects recruit the IPS when allocating spatial attention predictively. This alternate strategy may depend on enhancing receptivity to stimuli in unexpected locations, thus shifting to a more global exogenous attentional orienting that would rely more on IPS recruitment. Nevertheless, this strategy appears to

be less effective overall, as there was no benefit of informative cues on reaction time (comparison of valid vs. neutral cues) in the Sd state. These data suggest that sleep loss may affect performance by interfering with the ability to predictively allocate attention and to suppress distractibility to irrelevant spatial events. The consequence of this is that sleep-deprived individuals may miss predictive environmental cues and react impulsively to behaviorally irrelevant stimuli. Both responses are likely to increase errors and result in accidents even while individuals appear to be awake and responding.

Table S1.1: Cue Benefit Score Analysis (Activations by sleep state and contrast)

Sleep State and Brain Region	**MNI coordinates**			**Z score**	**# of voxels**
	x	**y**	**z**		
SO (CBS+)					
Posterior cingulate cortex	-12	-48	24	4.66	73
SO (CBS-)					
Left inferior parietal lobule	-30	-36	45	4.22	19
Sd (CBS+)					
hypothalamus	0	3	-3	4.15	13
Left thalamus	-18	-24	21	3.66	16
Sd (CBS-)					
Left Temporo-Occipital	-57	-51	12	3.87	10
Right Frontal eye fields	54	6	39	3.55	13
SO - Sd (CBS+)					
Right frontal eye fields	51	18	18	3.85	11
Posterior cingulate cortex	-3	-54	18	3.62	7*
Sd – SO (CBS+)					
Left intraparietal sulcus	-9	-57	60	4.86	12

* significant at small volume correction.

Table S1.2: V+ vs V- categorized by mean Invalid RT – 1 SE (Activations by sleep state and contrast)

Sleep State and Brain Region	**MNI coordinates**			**Z score**	**# of voxels**
	x	**y**	**z**		
SO (V^+ - V^-)					
Posterior cingulate cortex	-3	-57	24	4.46	98
Medial prefrontal cortex	0	42	36	3.99	14
SO (V^- - V^+)					
R Fusiform	30	-63	-21	4.32	23
R IPS	27	-69	51	3.87	14
Sd (V^+ - V^-)					
No significant activations					
Sd (V^- - V^+)					
Left Temporo-Occipital	-57	-51	12	3.87	10
Right Frontal eye fields	57	18	24	3.78	8#
Inferior frontal gyrus	45	30	-3	3.67	10
SO - Sd (V^+ - V^-)					
Right frontal eye fields	54	21	18	3.87	12
Left frontal eye fields	-57	15	18	3.89	9#
Posterior cingulate cortex	-9	-57	18	4.19	5*
Sd – SO (V^+ - V^-)					
No significant activations					

* significant at small volume correction, trend ($p < 0.1$) corrected across the entire brain.

Chapter 2: Age alters the neural response to sleep deprivation within the frontal cortex

Abstract

Intact functioning of frontal networks is critical for selecting appropriate responses, inhibiting inappropriate ones, and processing errors to employ appropriate behavioral corrections. Sleep deprivation and age impair these behaviors, but their interacting effects on frontal networks remain poorly understood. In the present report, we used functional magnetic resonance imaging (fMRI) while healthy young and old adults, in rested and sleep-deprived states, performed a go/no-go task containing components of response selection, error processing, and inhibition. Following sleep deprivation, young adults showed a greater increase in left ventrolateral prefrontal cortex activity for inhibition, a greater decrease in right superior frontal sulcus activity for response selection and a greater decrease in left insula activity for errors. In contrast, old adults showed a greater increase in anterior cingulate activity associated with errors. All regions where young adults showed a greater decrease in activity following sleep deprivation were already decreased at baseline in old adults. Decreased activity in response to age and sleep deprivation has been classically interpreted as decreased processing efficiency or impaired recruitment of neural resources, whereas increased activity has been interpreted to represent compensatory recruitment. In light of this, these data suggest that age and sleep deprivation impair processing in frontal networks similarly, but that compensatory responses to sleep deprivation may differ with age.

Introduction

Sleep deprivation affects many aspects of brain physiology, and functions of the frontal cortex may be especially affected (Chee & Choo, 2004; Chuah et al., 2006; Drummond et al., 2004; Falkenstein, Hoormann, & Hohnsbein, 2001; Habeck et al., 2004; Harrison & Horne, 1999; Harrison et al., 2000; Nessler, Friedman, Johnson, & Bersick, 2006). Behavioral studies have shown impaired frontal functions of response selection, response inhibition, and error processing following sleep deprivation (D. Dinges & Kribbs, 1991; Harrison & Horne, 1999; Harrison et al., 2000; Scheffers et al., 1999; Tsai et al., 2005).

Aging has been shown to impair a variety of frontal functions including inhibitory control, prepotent response inhibition, resistance to distracter interference, resistance to proactive interference, and error processing (Cohen, 1988; Falkenstein et al., 2001; Kausler & Hakami, 1982; McDowd & Filion, 1992; Nielson et al., 2002). Older adults also show less automatic and more controlled processing, requiring greater engagement of frontal regions including the anterior cingulate cortex on tasks that younger adults find non-demanding (Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005; R. West & Schwarb, 2006).

Disturbances of sleep architecture and quality are very common with aging, suggesting that the combination of sleep loss and aging may further affect frontal functioning (Feinberg & Carlson, 1968; Foley et al., 1995; Kales et al., 1967; Van Cauter et al., 2000). The interacting effects of sleep loss and aging have only been examined in

a few, predominantly behavioral studies (Adam et al., 2006; Bonnet & Arand, 1989; Bonnet & Rosa, 1987; Webb, 1985; Webb & Levy, 1982). In these studies, age-related differences were task dependent, suggesting that specific neural networks may be susceptible to the effects of age and sleep loss (Webb, 1985; Webb & Levy, 1982). Performance on tasks targeting frontal functioning in young, sleep-deprived adults is similar to that of rested old adults (Harrison et al., 2000). This finding suggests that age and sleep loss may have similar effects on frontal function. However, the neural correlates of sleep loss have not been examined across different age groups.

In order to determine how age and sleep loss affects prefrontal function we used behavioral measures and functional magnetic resonance imaging to examine young and old subjects performing a go/no-go task following sleep and 34-36 hours of sleep deprivation. Given that both age and sleep loss can impair inhibitory functioning, we expected that their interaction would lead to greater inhibitory impairments and alterations in recruitment of dorsal and ventral lateral prefrontal cortex, which is particularly associated with inhibitory task performance (Bellgrove et al., 2004; Booth et al., 2003; Garavan et al., 2002; Garavan et al., 1999; Horn et al., 2003; Konishi et al., 1999; Watanabe et al., 2002).

Results

Sleep Data

Sleep logs and wrist actigraphy verified that all subjects maintained an average of at least 7 hours of time in bed per night for at least five days before entering the GCRC. The amount of time in bed was similar in young and old adults before entering both

GCRC conditions (8.08±0.11 hours in young adults before the sleep opportunity (SO) condition versus 8.07±0.21 hours in old adults before the SO condition; and 7.69±0.21 hours in young adults before the sleep deprivation (Sd) condition versus 7.85±0.27 hours in old adults before the Sd condition).

GCRC PSG data showed that although total recording time (TRT) did not differ between young and old adults ($t_{16} = -0.67$, $p = 0.512$, 9.05±0.02 hours for young versus 9.07±0.02 hours for old), total sleep time was less in old adults ($t_{16} = 3.91$, $p = 0.001$, 7.89±0.15 hours for young versus 7.07±0.14 hours for old). Sleep latency was shorter in old adults ($t_{16} = 2.92$, $p = 0.010$, 28.97±3.80 min. for young versus 15.50±2.62 min. for old), but sleep efficiency was worse ($t_{16} = 3.38$, $p = 0.004$, 92.95%±1.17% for young versus 84.62%±2.17% for old) and WASO was greater ($t_{16} = -3.57$, $p = 0.003$, 5.54%±1.06% for young versus 14.43%±2.25% for old). There was no difference across age groups in the percentages of either stage 2 or REM sleep. However, young adults had a much greater percentage of slow wave sleep ($t_{16} = 5.76$, $p < 0.0001$, 11.90%±1.16% for young versus 2.75%±1.09% for old). For a table of results, see Table 3.1.

Behavioral Data

Sleep deprivation (Sd), as compared to a night of nine hours of sleep opportunity (SO), altered performance in young and old adults on a go/no-go task. A main effect of age group relating to percentage of correct responses (targets) was detected with young adults responding correctly more often than old adults (For "Age Group", $F_{1,16} = 4.648$, $p = 0.047$; for "Sleep Condition", $F_{1,16} = 3.459$, $p = 0.081$; for "Age Group × Sleep Condition", $F_{1,16} = 1.082$, $p = 0.314$, Figure 2.1A).

Percent of correct inhibitions was examined as a measure of inhibitory performance in both age groups and sleep conditions. There was a main effect of sleep condition, but not of age group or their interaction (For "Age Group", $F_{1,16} = 0.02$, $p = 0.883$; for "Sleep Condition", $F_{1,16} = 16.08$, $p = 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 1.10$, $p = 0.309$, Figure 2.1B). Two-sample t-tests using a Bonferroni *post hoc* correction for multiple comparisons revealed a significant difference ($p < 0.05$) between the SO and Sd conditions for both age groups, with both age groups having better inhibitory performance in the SO condition.

In order to examine the effects of age and sleep condition on both response selection and response inhibition performance, a measure of response bias, d', was calculated from the proportions of correct responses, correct inhibitions, misses (errors of omission), and false alarms (errors of commission) (Green & Swets, 1966). A main effect of sleep condition, and an interaction effect of age by sleep condition relating to performance accuracy were detected (For "Age Group", $F_{1,16} = 3.58$, $p = 0.077$; for "Sleep Condition", $F_{1,16} = 16.18$, $p = 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 5.27$, $p = 0.036$, Figure 2.1C). Young adults responded significantly more accurately than old adults after a nine-hour night of sleep opportunity; however, young adults also showed a significant decrement in their response accuracy following sleep deprivation. This result is consistent with prior studies showing greater drop in younger adults' performance after sleep deprivation (Adam et al., 2006; Webb, 1985; Webb & Levy, 1982).

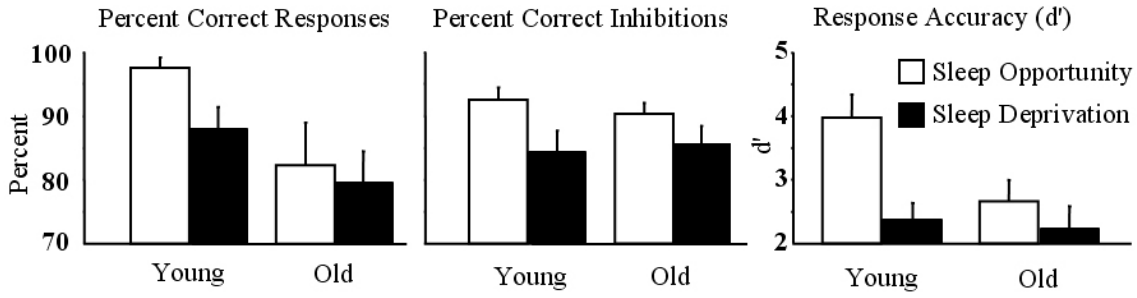

Figure 2.1. Go/No-Go task performance by age and sleep condition. Percentage of correct responses **(a)** and correct inhibitions **(b)** after a night of nine hours of sleep opportunity (white) and a night of sleep deprivation (black) are presented for young and old adults. Response accuracy metric d' **(c)** after a night of nine hours of sleep opportunity (white) and a night of sleep deprivation (black) is presented for young and old adults.

fMRI Data

ROI analysis

Response Inhibition (Correct Inhibitions – Targets Contrast)

No age by sleep deprivation interactions were detected within any of the right prefrontal VOIs or at the whole brain level, suggesting that the interaction of age and sleep deprivation on brain activation occurs outside the right prefrontal cortex. Examination of mean activation within VOI-1 [x = 45, y = 6, z = 27, 137 voxels] demonstrated an effect of age, but no effect of sleep condition or an age by sleep condition interaction (For "Age Group", $F_{1,16} = 10.978$, $p = 0.004$; for "Sleep Condition", $F_{1,16} = 1.308$, $p = 0.270$; for "Age Group × Sleep Condition", $F_{1,16} = 1.095$, $p = 0.311$, Figure 2.2A). These data suggest that young adults recruit this region more than old adults, but that sleep deprivation does not affect activity in this region.

Examination of mean activation within VOI-2 [x = 36, y = 21, z = 6, 349 voxels] demonstrated a main effect of age and sleep condition, but no interaction effect (For "Age Group", $F_{1,16} = 6.208$, $p = 0.024$; for "Sleep Condition", $F_{1,16} = 8.575$, $p = 0.010$; for "Age Group × Sleep Condition", $F_{1,16} = 0.013$, $p = 0.909$, Figure 2.2B). These data suggest that activity in this region is reduced in old adults, and that sleep deprivation reduces activity in this region similarly in young and old adults.

Finally, examination of mean activation within VOI-3 [x = 39, y = 36, z = 27, 68 voxels] demonstrated a main effect of sleep condition, but no main effect of age or interaction effect (For For "Age Group", $F_{1,16} = 0.627$, $p = 0.440$; for "Sleep Condition", $F_{1,16} = 5.598$, $p = 0.031$; for "Age Group × Sleep Condition", $F_{1,16} = 1.737$, $p = 0.206$,

Figure 2.2C). These data suggest that activity in this region is reduced by sleep deprivation similarly in young and old adults.

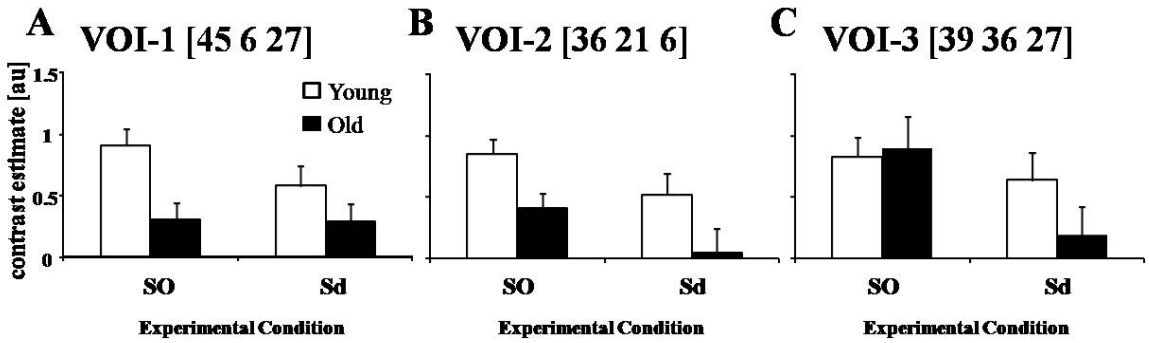

Figure 2.2. Activation during response inhibition events (correct inhibitions – targets contrast) within three prefrontal volumes of interest (VOI) in young (white bars) and old (black bars) adults in sleep opportunity and sleep deprivation conditions is presented. Mean contrast estimates were extracted for each cluster with maxima located at xyz coordinates [45 6 27] for VOI-1 **(a),** [36 21 6] for VOI-2 **(b)**, and [39 36 27] for VOI-3 **(c)**. All values are presented as Mean±SEM.

Whole brain analysis

Response Inhibition (Correct Inhibitions – Targets Contrast)

Regions outside the right prefrontal cortex were examined using whole brain analysis. When examining the BOLD response associated with response inhibition, young and old adults recruited a distributed network of ventral lateral prefrontal, inferior parietal and fusiform regions as observed in many other studies of inhibitory control, Table 2.2 (Bellgrove et al., 2004; Booth et al., 2003; Garavan et al., 2002; Garavan et al., 1999; Nielson et al., 2002; Rubia et al., 2001; Watanabe et al., 2002). Young adults also showed a significant increase in activity from baseline within the left dorsal lateral prefrontal cortex following sleep deprivation, Tab1e 2.2: A7. Old adults did not show increased recruitment of left prefrontal regions when sleep-deprived. This was detected as a significant age by sleep condition interaction, Table 2.1, Figure 2.3B.

To determine how this increased activity related to performance, contrast estimates were extracted from this region using MarsBaR analysis tool box (see methods). Surprisingly, greater activation in this dorsal lateral prefrontal region related to fewer lapses but not better inhibitory performance. This relationship was a trend in the SO condition (Spearman's rho: 0.630, $p = 0.069$), but was significant in the Sd condition (Spearman's rho: 0.728, $p = 0.026$).

Motor Output (Targets – Correct Inhibitions Contrast; inverse of response inhibition contrast)

In both conditions and age groups, this contrast resulted in the recruitment of left primary motor cortex, Table 2.3. There were no significant age, sleep deprivation, or age by sleep deprivation effects.

Error Processing (Errors – Targets Contrast)

For error processing, rested young adults showed activation of dorsal anterior cingulate gyrus, bilateral insula, and bilateral temporo-parietal junction whereas old adults recruited dorsal anterior cingulate, anterior temporal, and brainstem regions, Table 2.4: A1,3,5,7, and 9; B1,4 and 6. Recruitment of dorsal anterior cingulate and bilateral insula following a night of sleep was greater in young than old adults, Table 2.4: C1-3. Following sleep deprivation, young adults showed a reduction in recruitment of the left insula activation, but similar recruitment of dorsal anterior cingulate, right insula, and bilateral temporo-parietal junction activation, Table 2.4: A6, A2, 4, 8, and 10 respectively. Old adults showed an increased activation within the anterior cingulate cortex, Table 2.4: B3. Both the insula and anterior cingulate effects were detected as significant age by sleep condition interactions, Table 2.1, Figure 2.3C-D.

Response Selection (Targets – Errors Contrast; inverse of error processing contrast)

For the response selection contrast, young adults recruited bilateral superior frontal sulcus following a night of sleep as expected, Table 2.5: A1-2 (Heekeren et al.,

2004; Heekeren et al., 2006; Rowe et al., 2000). Activity in these regions was also greater in rested young than old adults, Table 2.5: C1-2. In contrast, old adults showed activation of ventral medial prefrontal cortex, Table 2.5: B1. Following sleep deprivation, activity in right superior frontal sulcus was reduced in younger adults as compared to following a night of sleep, Table 2.5: A3. Reduced right superior frontal activity following sleep deprivation in young adults was greater than that observed in old adults. This effect was detected as an age by sleep condition interaction, Table 2.1, Figure 2.3A.

Table 2.1: Age × Sleep condition interactions

Age and Brain Region	Sleep State	MNI Coordinates			z score	voxel #
		x	y	z		
Correct inhibitions – Targets (Res. Inhib.)						
Young > Old						
L ventral lateral prefrontal cortex	Sd-SO	-30	15	39	4.59	167
Errors – Targets (Er .Proc.)						
Young > Old						
L insula	SO-Sd	-36	9	3	3.83	108
Old > Young						
R dorsal anterior cingulate	Sd-SO	6	15	18	4.24	146
Targets – Errors (Res. Sel.)						
Young > Old						
R superior frontal sulcus	SO-Sd	33	27	54	4.48	90

Table 2.2: Correct inhibitions – Targets (Response Inhibition)

Age and Brain Region		Sleep State	MNI Coordinates			z score	voxel #
			x	y	z		
Young							
A1	R ventral lateral prefrontal cortex	SO	36	21	6	4.47	349
A2		SO	45	6	27	4.95	137
A3		Sd	36	33	18	3.77	93
A4		Sd	48	-3	36	3.73	78#
A5	L dorsal lateral prefrontal cortex	SO	-48	-3	48	4.47	83#
A6		SO	-39	3	24	4.35	101
A7		Sd-SO	-27	18	36	4.65	175
A8	R superior frontal gyrus	SO	36	3	63	4.21	129
A9	R dorsal anterior cingulate	Sd	6	15	51	4.41	410
A10	R inferior parietal lobule	SO	36	-48	51	5.17	294
A11		Sd	33	-57	51	5.19	192
A12	L inferior parietal lobule	Sd	-27	-69	33	4.18	81#
A13	R fusiform gyrus	SO	48	-72	-9	4.82	357
A14	L fusiform gyrus	SO	-45	-66	-3	6.69	500
A15		Sd	-45	-57	-9	5.06	219
A16	L middle occipital gyrus	SO	-27	-78	24	4.39	77#
Old							
B1	R ventral lateral prefrontal cortex	SO	39	36	27	3.76	68#
B3	R fusiform gyrus	SO	45	-51	-15	4.36	65#
B4		Sd	45	-54	-18	5.02	243
B5	L fusiform gyrus	SO	-48	-63	-15	4.79	222
B6		Sd	-36	-60	-6	4.60	332

Trend: $p < 0.1$ corrected

Table 2.3: Targets – Correct Inhibitions (Motor Output)

Age and Brain Region		Sleep State	MNI Coordinates			z score	voxel #
			x	y	z		
Young							
A1	L primary motor cortex	SO	-36	-21	69	5.07	401
A2		Sd	-30	-24	48	3.73	84
A3	superior temporal gyrus	SO	-51	-21	12	4.74	91
A4	bilateral posterior cingulate cortex	SO	3	-63	27	3.90	125
Old							
B1	L primary motor cortex	SO	-42	-27	48	5.25	530
B2		Sd	-54	-30	27	3.75	74#
B3	bilateral midline cingulate cortex	SO	-3	-21	45	4.83	198

Trend: $p < 0.1$ corrected

Table 2.4: Errors-Targets (Error Processing)

Age and Brain Region		Sleep State	MNI Coordinates			z score	voxel #
			x	y	z		
Young							
A1	dorsal anterior cingulate	SO	-3	24	30	6.21	782
A2		Sd	3	21	51	6.99	892
A3	R insula	SO	42	21	0	7.01	744
A4		Sd	42	21	6	6.04	530
A5	L insula	SO	-39	12	-3	6.93	854
A6		SO-Sd	-30	12	6	5.02	311
A7	R temporal-parietal junction	SO	60	-42	36	4.67	315
A8		Sd	63	-48	36	4.83	222
A9	L temporal-parietal junction	SO	-57	-42	36	4.37	225
A10		Sd	-66	-48	30	4.73	124
Old							
B1	dorsal anterior cingulate	SO	6	27	48	4.13	118
B2		Sd	-12	30	30	4.02	214
B3		Sd-SO	6	15	15	4.04	71#
B4	L anterior temporal pole	SO	-42	12	-27	4.01	87
B5		SO-Sd	-45	-12	-18	4.40	118
B6	brainstem	SO	-3	-30	-30	4.21	79
B7	R ventral lateral prefrontal cortex	Sd	45	18	3	3.83	141
Young > Old							
C1	dorsal anterior cingulate	SO	3	24	27	4.56	248
C2	R insula	SO	45	18	-9	4.21	166
C3	L insula	SO	-42	9	-3	5.28	351

Trend: $p < 0.1$ corrected

Table 2.5: Targets – Errors (Response Selection)

Age and Brain Region		Sleep State	MNI Coordinates			z score	voxel #
			x	y	z		
Young							
A1	L superior frontal sulcus	SO	-24	39	48	4.72	212
A2	R superior frontal sulcus	SO	21	39	51	4.44	145
A3		SO-Sd	24	39	48	4.21	204
A4	R occipital cortex	Sd	24	-96	3	4.67	194
A5	R thalamus	Sd	21	-15	27	4.11	78#
Old							
B1	ventral medial prefrontal cortex	SO	-12	24	9	4.49	416
B2	R parahippocampal gyrus	Sd	30	-33	-27	4.21	69#
Young > Old							
C1	L superior frontal sulcus	SO	-39	15	54	4.55	94
C1	R superior frontal sulcus	SO	33	27	54	4.61	134

Trend: $p < 0.1$ corrected

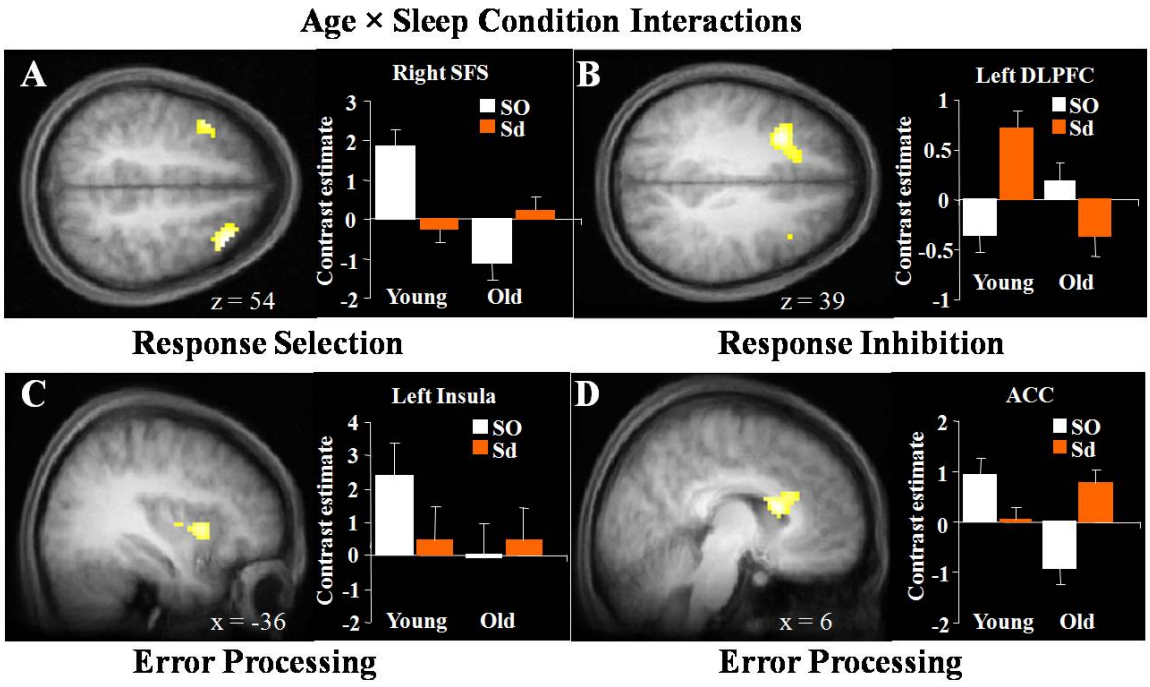

Figure 2.3. Activation related to a significant age by sleep condition interaction within networks of response selection **(a)**, response inhibition **(b)**, and error processing **(c-d)**. **A)** Response selection network (Target – Errors contrast). Contrast estimates for young and old adults at xyz coordinates [33 27 54] are presented for the SO condition (white bars) and SD condition (orange bars). Right superior frontal sulcus activation is greater in the sleep opportunity condition than the sleep deprivation condition for young adults but not old adults. **B)** Response inhibition network (Correct inhibitions – Targets contrast). Contrast estimates for young and old adults at xyz coordinates [-30 15 39] are presented for the SO condition (white bars) and SD condition (orange bars). Left middle frontal gyrus activation is greater in the sleep deprivation condition than the sleep opportunity condition for young adults but not old adults. **C)** Error processing network (Errors – Targets contrast). Contrast estimates for young and old adults at xyz

coordinates [-36 9 3] are presented for the SO condition (white bars) and SD condition (orange bars). Left anterior insula activation is greater in the sleep opportunity condition than the sleep deprivation condition for young adults but not old adults. **D)** Error processing network (Errors – Targets contrast). Contrast estimates for young and old adults at xyz coordinates [6 15 18] are presented for the SO condition (white bars) and SD condition (orange bars). Dorsal anterior cingulate activation is greater in the sleep deprivation condition than the sleep opportunity condition for old adults but not young adults. All peaks are significant at $p < 0.05$ corrected across the entire brain volume at the cluster level.

VBM Data

No age-related changes in gray-matter volume were detected. However, the sample size in the current study is relatively small, thus small group differences in gray matter volume may not have been detected.

Discussion

The results of this study demonstrate, for the first time, that while performing a go/no-go task, the effects of sleep deprivation on brain activity differs with age. Age altered response selection, inhibition, and error-related neural responses to sleep deprivation in regions outside the ventral lateral prefrontal cortex. Specifically, following sleep deprivation, young adults showed greater reductions in recruitment of right superior frontal sulcus activation during response selection events, greater increases in recruitment of left middle frontal gyrus activation during inhibition events, and greater reductions of left insula activation during error events. In contrast, sleep-deprived old adults showed greater increases in recruitment of dorsal anterior cingulate activation during error events. Decreased activity in response to age and sleep deprivation has been classically interpreted as decreased processing efficiency or impaired recruitment, whereas increased activity has been interpreted to represent compensatory recruitment (Cabeza, 2002; Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 1999; Grady, 1998; Grady et al., 1998; Langenecker & Nielson, 2003; Nielson et al., 2002). In light of these interpretations, it is possible that age alters both where sleep deprivation

impacts processing efficiency and where sleep deprivation elicits a compensatory response.

We predicted that age and sleep deprivation would interact to produce greater impairments of inhibitory performance and greater alterations in right ventral lateral prefrontal recruitment. To our surprise, inhibitory performance was similar across age groups in both sleep opportunity and sleep deprivation conditions. The lack of age differences in baseline inhibitory performance may be due to the sample of old adults in the current study being more cognitively healthy than older adults in other studies of inhibitory functioning. Previous studies of the effects of age on inhibitory function, suggest that performance differences can be subtle (Nielson et al., 2002). Corresponding to this, old adults showed reduced right prefrontal activation in two of the three volumes of interest. Sleep deprivation impaired recruitment of right ventral prefrontal activity within two of the three volumes of interest; those that were more anterior in location. Activation in these regions was reduced similarly by sleep deprivation in both age groups. Correspondingly, when sleep-deprived, both age groups showed significant impairments in inhibitory performance. These data demonstrate that right prefrontal activity is less likely to be the source of age by sleep deprivation interaction effects on performance. Instead, other regions outside the right prefrontal cortex must result in age by sleep deprivation interactions. This makes sense, given that the age by sleep deprivation interaction on performance was with regard to response accuracy and not inhibitory ability per se.

Sleep deprivation reduced activations in young adults in regions where older adults already showed decreased activation at baseline, e.g. within right dorsal and ventral prefrontal cortex and left insula. From this, we could suggest that age and sleep deprivation impair cortical functioning similarly, particularly within the right prefrontal cortex. This interpretation has been suggested in previous reports (Chee & Choo, 2004; Choo et al., 2005; Grady et al., 2006; Habeck et al., 2004; Harrison et al., 2000; Persson et al., 2007). However, there are distinct differences in the response between age and sleep deprivation. In the current report, age impaired left dorsal prefrontal recruitment, but sleep deprivation did not appear to do so. In fact, sleep deprivation resulted in the increased recruitment of left prefrontal activation. Additionally, age impaired activation within dorsal anterior cingulate and right insula, but sleep deprivation did not appear to do so. Moreover, old adults actually increased anterior cingulate activation following sleep deprivation. It appears that, when compared to the effects of age, sleep deprivation has similar yet distinct effects on cortical functioning. These effects interact to produce differential neural responses to sleep deprivation in young and old adults. This differential response appears to reflect a greater dorsal prefrontal susceptibility to aging effects and a greater right prefrontal susceptibility to sleep deprivation effects.

With regards to dorsal prefrontal susceptibility with age, these data are consistent with previous reports. A report by Rypma and D'Esposito suggests the age-dependent decline in working memory performance is due to effects on retrieval processes dependent on dorsal prefrontal regions (Rypma & D'Esposito, 2000). Additionally, age-related reductions in gray matter volume occur most dramatically within the dorsal

prefrontal cortex (Sowell et al., 2003), though voxel-based morphometry revealed no significant age difference in the current sample. These data support the data in the current report that suggest age impacts dorsal prefrontal functioning.

It has been suggested that right prefrontal cortex is important for the maintenance of the alert state (Posner, 1994). The data from the current report suggest that when individuals are deprived of sleep, right prefrontal recruitment is reduced, and this results in an increase in both commission and omission errors. It should be noted that the data do not imply the absence of an age effect on ventral prefrontal processes, or a sleep deprivation effect on left prefrontal functioning, rather within the context of this task, age appears to exert greater effects on dorsal frontal regions and sleep deprivation appears to exert greater effects on right prefrontal cortex.

Just as age and sleep deprivation impact brain activation differentially, they also impact performance differentially. Old adults performed as well as young adults when inhibiting responses after a night of sleep. After sleep deprivation, both young and old adults also decline similarly in terms of inhibitory performance. These data show that age and sleep deprivation have differential effects on inhibitory performance. Further, the ability to respond to the appropriate target stimulus and overall performance accuracy were impaired by both age and sleep deprivation. Sleep deprivation led to a greater impairment of response selection performance in the young, probably because they had a higher baseline performance in the rested state. Hence, in terms of performance, some cognitive abilities are affected similarly by sleep deprivation across ages while others are not.

Over the last several decades, numerous reports have suggested that sleep deprivation results in the increased likelihood of generating errors of omission and commission, e.g. not responding during go events and responding during no-go events (D. Dinges & Kribbs, 1991). Indeed, the increased likelihood of producing both of these errors is generally thought of as being characteristic of sleep deprivation. A recent report has shown that sleep deprivation results in a reduction of the error negativity (N_e) which is accompanied with an impairment in error-remedial actions (Tsai et al., 2005). Aging also has been shown to result in similar performance impairments (Cohen, 1988; Falkenstein et al., 2001; Kausler & Hakami, 1982; McDowd & Filion, 1992; Nessler et al., 2006; Nielson et al., 2002). Thus, it is not surprising that following sleep deprivation young subjects show a greater drop in performance accuracy, a greater loss of right superior frontal sulcus activity during response selection and a greater loss of left insula activity during errors. Old adults are already impaired in terms of performance after a night of sleep, and already show reduced recruitment of bilateral superior frontal sulcus during response selection and reduced recruitment of dorsal anterior cingulate and bilateral insula during errors.

It has been posited that young and old adults perform the same task differently in terms of the utilization of brain resources (Grady, 1998). Since young and old adults showed increased activation in different regions associated with different cognitive processes, we can suggest that young and old adults might utilize different compensatory strategies in the face of sleep deprivation. Age resulted in reduced superior frontal activation and the presence of ventral medial prefrontal cortex activation during response

selection events. Ventral medial prefrontal regions are associated with decision-making processes (Bechara et al., 2000), and dorsal prefrontal regions are sensitive to age effects (Rypma & D'Esposito, 2000). It is possible old adults, being less able to utilize dorsal prefrontal cortex, rely on ventral medial prefrontal regions for response selection abilities. It is also possible that older adults exhibit more disinhibition of the so called 'default mode' network, which includes the ventral medial prefrontal cortex (Gusnard et al., 2001). This is evidenced in the sleep deprivation condition, when old adults exhibit an increase in anterior cingulate activation from baseline during errors. This could reflect an age related increase in the susceptitibility of default mode disinhibition caused by stressors such as sleep deprivation. Alternatively, this activation may reflect a compensatory activation related to processing erroneous responses in order to enact error remedial behavior.

Younger adults showed increased recruitment of left ventral lateral prefrontal cortex during inhibition events after sleep deprivation. Increased recruitment of left ventral lateral prefrontal cortex has been observed following sleep deprivation on tasks of working memory and divided attention (Chee & Choo, 2004; Drummond et al., 2001). This has been interpreted to reflect a compensatory response, though it is unclear whether this is task specific or reflects a general ramping up of the attention or working memory systems. If recruitment of left ventral lateral prefrontal cortex in the present study was associated with the latter explanation, one would expect left frontal recruitment to be associated with both inhibition and target events, since both reflect accurate performance and have similar attentional and working memory demands. At first glance, it would

seem left dorsal lateral prefrontal recruitment is most likely related to inhibitory control, as its recruitment is greater during inhibitory events than target events. However, recruitment of this region related more to a minimization of lapses than inhibition errors. These data argue more for increased recruitment of response selection related attention and working memory processes specifically during inhibition events, which may aid in maintaining correct stimulus-response associations for go as well as no-go events. Others have shown an enhancement of spatial attention during inhibition events (Maguire et al., 2003). Therefore, increased activation in response to sleep deprivation depends on cognitive event and age, with young, sleep-deprived subjects relying on left dorsal lateral prefrontal regions, and old adults relying on ventral medial prefrontal regions. Further, sleep-deprived, old adults recruited more dorsal anterior cingulate activity during errors. It may be that when sleep-deprived, young adults rely on recruiting frontal networks involved with enhancing spatial attention related to inhibitory functioning, whereas old adults may rely more on recruiting regions associated with processing erroneous responses.

No effects of age or sleep deprivation were detected within unimodal sensory or motor regions such as within the primary motor cortex or fusiform gyrus (motor output contrast). These data suggest that the effects of age, sleep deprivation, and their interaction on go/no-go performance is more dependent on changes within regions associated with adapting motor responses to be contextually dependent behaviors. Although it is possible that the study was underpowered to detect subtle differences within primary motor or sensory areas, the results also highlight the greater sensitivity of

prefrontal regions to the effects of aging and sleep loss (Harrison et al., 2000; R. L. West, 1996). Most studies of sleep deprivation have observed similar effects (Chee & Choo, 2004; Choo et al., 2005; Chuah et al., 2006; Drummond et al., 2000; Drummond et al., 2004).

Activation within association cortex (predominantly prefrontal, cingulate, inferior parietal, and temporo-parietal) is reduced during non-rapid eye movement sleep, particularly within the right hemisphere (NREM) (Braun et al., 1997; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). It is commonly thought that following sleep deprivation, lapses represent briefs transitions into NREM sleep or "microsleeps" (D. Dinges & Kribbs, 1991). Therefore, it could be that it isn't prefrontal cortex, per se, that is more affected by sleep loss, but association cortex as a whole. The idea that these multimodal and transmodal association cortices translate sensory inputs into conscious experience has been proposed (Mesulam, 1998). Thus, it may not be surprising that activity within these areas is reduced in the transition into NREM sleep, a period without conscious experience. Thus, sleep deprivation may result in the intermittent suppression of these cortical regions, which could impair their functioning even during periods where the sleep-deprived individual is awake and responding. Though interesting, this issue cannot be addressed in the current report. Future reports will benefit from combining measures of wake EEG and fMRI in order to examine the relationship between lapses, microsleeps, and suppression of multimodal association cortex.

In terms of both performance and brain activity, many of the age by sleep condition effects were due to young adults falling from a higher baseline. It is possible

that baseline differences occur, not just because of aging effects alone, but due to residual effects of sleep loss in the old adults. Indeed, though they did not report being sleepier on either the Pittsburgh Sleep Quality Index or the Epworth Sleepiness Scale, they had reduced total sleep time. This is true even though they had a similar time in bed. Changes in sleep architecture are common in aging, particularly with regard to a reduction in total sleep time (Feinberg & Carlson, 1968; Kales et al., 1967; Van Cauter et al., 2000). It is possible that old adults had sleep loss-related performance impairments that contributed to the age effect. A study of prefrontal function in young and old adults showed that old adults performed similarly as sleep-deprived young adults (Harrison et al., 2000). The current data suggest, however, that though there are similarities between the effects of age and sleep deprivation, their effects are not identical.

The present study has limitations. In the present study, there were only nine subjects per group. A larger sample size would have increased our power to detect group differences, but significant group differences were still detected using a conservative statistical threshold. Like other small functional imaging studies of aging and sleep loss, these data offer important insights into the effects of aging and sleep deprivation on brain function, which outline the differential sensitivity of dorsal frontal and right prefrontal regions (Chuah et al., 2006; Nielson et al., 2002). Additionally, the small number of commission errors made at baseline by each individual may have impacted the reliability of error-related activations. However, subjects averaged between twenty to thirty events per sleep condition. A study by Murphy and colleagues demonstrated that minimal differences were present even between 25 and 150 trial events in terms of activation

extent and reliability of activation (Murphy & Garavan, 2005). In addition, in the present study, no significant correlation was found between activation and number of error events in any brain region (data not shown). Future studies will have to utilize task paradigms where number of error events is made equivalent to number of successful inhibition events in order to address the issue of reliability.

These data demonstrate, for the first time, that the effects of sleep deprivation on neuronal physiology are age-dependent and concordant with the age-dependent behavioral effects of sleep deprivation. Sleep deprivation impairs performance and alters brain function within multiple prefrontal networks relating to the cognitive control of motor responses in an age-dependent manner. The alterations in performance accuracy and brain activation following sleep deprivation are similar and yet distinct from those observed with age. Age appears to preferentially impair recruitment within dorsal prefrontal and anterior cingulate regions, and sleep deprivation appears to preferentially impair recruitment within right dorsal and ventral lateral prefrontal regions. The interaction of age and sleep deprivation changes the responsiveness within distinct frontal regions associated with distinct frontal-dependent behaviors. Furthermore, it appears that regardless of age, at least while performing a task requiring context specific responses, sleep deprivation alters functioning predominantly within brain regions associated with adapting motor responses to become context specific behaviors. Finally, mechanisms of compensation for sleep loss may differ with age. This has implications for managing sleep loss, in that what cognitive and neural resources young adults utilize to maintain optimal performance may not be what old adults utilize. Larger studies will be needed to

examine a variety of prefrontal-dependent behaviors in order to isolate more carefully the heterogeneous effects of sleep deprivation and age on brain function.

Chapter 3: Age alters neural responses associated with recovery from sleep deprivation within the prefrontal cortex

Abstract

The prefrontal cortex controls a variety of context-dependent behaviors such as response inhibition. Sleep deprivation has been shown to impair these abilities and alter related brain activity within the prefrontal cortex. The process of recovery from sleep deprivation is poorly understood, but one study suggests that prefrontal activity is not returned to normal following one night to recover from sleep deprivation (Wu et al., 2006). Age also impairs prefrontal functioning; however, no studies have used functional imaging techniques to directly compare neural responses to recovery from sleep deprivation in young and old adults. Here we compare the effects of one night of sleep following sleep deprivation on go/no-go task performance and related prefrontal activation in young and old adults using functional magnetic resonance imaging. A reduction in right prefrontal cortex activity was observed from the sleep opportunity to the sleep recovery condition in both young and old adults, suggesting that impaired right prefrontal recruitment persists after one night of recovery sleep. In addition, young adults show a greater increase in left prefrontal activation than old adults following recovery sleep. However, this left prefrontal difference was probably due to the fact that older adults had greater left prefrontal recruitment at baseline which was reduced after recovery sleep. Right prefrontal activation was associated negatively with inhibitory performance in young adults and positively associated in old adults. These data suggest

that one night of sleep following sleep deprivation is not sufficient to return neural responses to baseline, and that age may alter the neural correlates of recovery processes. Comparison with EEG data following recovery sleep suggests that where young adults may rely more on delta power to recover recruitment of right prefrontal activation, old adults may rely more on sigma power to recruit alternative regions.

Introduction

For over a hundred years, studies have explored the detrimental effects of sleep loss on cognitive functioning. Relatively few studies have explored the process of recovery from sleep deprivation. It has been known for decades that the amount of sleep gained upon recovery from sleep deprivation is never as much as was lost (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970). In spite of this, cognitive performance is generally no longer impaired after one or two nights of sleep to recover from sleep deprivation, though it remains unclear how cognitive recovery is achieved (Bonnet, 1985; Gosselin et al., 2005; Patrick & Gilbert, 1896; Rosa et al., 1983; Williams et al., 1959). An aspect of the behavioral definition of sleep is that sleep deprivation is followed by a rebound of sleep that is more intense (Carskadon & Dement, 1994; Durmer & Dinges, 2005; Kleitman, 1963). Characteristics of this increased intensity are; reduced responsiveness to the environment in comparison to normal sleep, altered electroencephalographic properties of sleep (such as higher spectral power in the delta frequency), and increased sleep time and efficiency (Blake & Gerard, 1937; Borbely et al., 1981; Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970; Kleitman, 1963; Patrick & Gilbert, 1896; Pieron, 1913). This appears to be the case even in older adults,

though to a lesser degree (Bonnet, 1986; Carskadon & Dement, 1985; Reynolds et al., 1986).

The specifics of performance recovery appear less characterized and depend on the method of sleep deprivation (total sleep deprivation versus recurrent sleep restriction), the duration of sleep recovery bouts, and the task performed (Belenky et al., 2003; Bonnet, 1985; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Patrick & Gilbert, 1896; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). When given one night with 8 hours time in bed, studies generally show that impairments can persist for anywhere between one and three days (Belenky et al., 2003; Herscovitch & Broughton, 1981; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). This appears to be true for older adults as well (Bonnet, 1985). A night of ten or more hours in bed appears to result in mostly recovered performance in a single night, though some subtle differences may still remain (Bonnet, 1985; Gosselin et al., 2005; Herscovitch et al., 1980; Patrick & Gilbert, 1896).

As may be expected, residual performance impairments after recovery tend to be the same types of performance impairments that are the most severe after sleep deprivation, e.g. reaction time slowing, cognitive slowing, and increased false alarm rate (Belenky et al., 2003; Bonnet, 1985; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). These are impairments of attention and executive functioning, which rely on frontal-parietal networks (Cabeza & Nyberg, 2000; Mesulam, 1986). The prefrontal cortex is particularly sensitive to sleep loss (Harrison et al., 2000; Thomas et al., 2000).

It is likely that prefrontal functions may also take the longest to recover, enabling residual performance impairment for days following recovery from sleep deprivation. Indeed, a recent report has shown that metabolic activity within the prefrontal cortex has not yet returned to baseline levels after one night to recover (Wu et al., 2006).

Age can also impair prefrontal functioning in a similar manner and sleep loss is common in aging (Feinberg & Carlson, 1968; Foley et al., 1995; Harrison et al., 2000; Kales et al., 1967; Monjan, 1990; Van Cauter et al., 2000; R. L. West, 1996). Thus, it becomes important to determine whether or not age interacts to alter the recovery process. The effects of age on performance recovery show mixed results (Bonnet & Arand, 1989). A comparison of the data from Wu and colleagues and Smith and colleagues suggest that brain function following recovery from sleep deprivation is altered by age (G. S. Smith et al., 1999; Wu et al., 2006). However, no studies have directly compared the neural response to recovery in young and old adults.

Here we compare the effects of one night of sleep following sleep deprivation (SR) to a baseline night of nine hours of sleep opportunity (SO) on go/no-go task performance and related prefrontal activation in young and old adults using functional magnetic resonance imaging. We further examine whether changes in spectral power in the delta and sigma bands during non-rapid eye movement (NREM) sleep following sleep deprivation relates to changes in activation from baseline to recovery conditions.

Results

PSG Data

PSG data are shown in Table 3.1. Total recording time (TRT) did not differ between young and old adults in either SO or SR conditions, and, as expected, TRT differed between SO and SR conditions similarly in both groups (For "Age Group", $F_{1,16} = 0.28$, $p = 0.606$; for "Sleep Condition", $F_{1,16} = 1429.70$, $p < 0.0001$; for "Age Group × Sleep Condition", $F_{1,16} = 0.005$, $p = 0.946$). Total sleep time (TST) was less in old adults in both conditions, but sleep increased similarly following sleep deprivation (For "Age Group", $F_{1,16} = 45.60$, $p < 0.001$; for "Sleep Condition", $F_{1,16} = 174.50$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 0.90$, $p = 0.346$); young adults increased sleep an average of 111 minutes and old adults increased sleep an average of 96 minutes. Sleep latency was shorter in old adults than young adults in the sleep opportunity condition, but both age groups had similar sleep latencies after sleep deprivation (For "Age Group", $F_{1,16} = 4.32$, $p = 0.054$; for "Sleep Condition", $F_{1,16} = 34.97$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 9.82$, $p = 0.006$). The presence of an interaction suggests that sleep deprivation results in a larger decrease in sleep latency in young adults. Sleep efficiency was worse in old adults in both conditions, but sleep efficiency increased similarly in both groups (For "Age Group", $F_{1,16} = 20.21$, $p < 0.001$; for "Sleep Condition", $F_{1,16} = 27.91$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 0.40$, $p = 0.538$). Wake after sleep onset (WASO) was greater in old adults in both conditions (SO and SR), and in fact, remained higher after sleep deprivation than young adults during the sleep opportunity condition (For "Age Group", $F_{1,16} = 21.46$, $p < 0.001$; for "Sleep Condition", $F_{1,16} = 27.27$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 0.63$, $p = 0.440$). The change in WASO

following sleep deprivation was similar in magnitude and direction in both age groups. There was a trend for a larger percentage of stage 2 sleep in old adults, and as previously shown, young adults show reduced stage 2 sleep percentage after sleep deprivation (For "Age Group", $F_{1,16} = 3.86$, $p = 0.067$; for "Sleep Condition", $F_{1,16} = 0.283$, $p = 0.602$; for "Age Group × Sleep Condition", $F_{1,16} = 7.92$, $p = 0.012$; (H. W. Agnew, Jr. et al., 1964; Borbely et al., 1981; Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970)). Interestingly, old adults showed increased stage 2 sleep percentage, and this was represented as a significant interaction effect in the present data. However, it is important to note that slow waves in old adults have reduced amplitude, and thus some slow waves would not surpass the slow wave criteria put forth by Rechtschaffen and Kales (Dijk et al., 1989; Rechtschaffen & Kales, 1968). Thus, increases in slow waves may be scored as increases in stage 2 in old adults. Young adults had a much greater percentage of slow wave sleep, and they increased SWS to a greater degree following sleep deprivation (For "Age Group", $F_{1,16} = 24.88$, $p < 0.001$; for "Sleep Condition", $F_{1,16} = 40.63$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 6.39$, $p = 0.022$). Because of this issue, spectral analysis of EEG data becomes essential when examining age differences (Dijk et al., 1989). Finally, there was no difference across age groups in the percentages of REM sleep, nor was there an effect of sleep deprivation on REM sleep percentage. However, given the literature, it is likely had we recorded sleep for a second night following sleep deprivation, we would have observed a rebound in REM sleep (W. Dement, 1960; Kales et al., 1970; Webb & Agnew, 1965).

Table 3.1. Sleep Variables

PSG Variable	Baseline	SR	$F_{1,16}$ (A)	$F_{1,16}$ (C)	$F_{1,16}$ (A×C)	p_A	p_C	$p_{A\times C}$
TRT (hours)			0.28	1429.70	0.005	0.606	<0.0001	0.946
Young	9.05(0.02)	10.08(0.03)						
Old	9.07(0.02)	10.09(0.04)						
TST (hours)			45.60	174.50	0.90	<0.001	<0.001	0.346
Young	7.89(0.15)	9.74(0.05)						
Old	7.07(0.14)	8.67(0.17)						
Latency (min.)			4.32	34.97	9.82	0.054	<0.001	0.006
Young	28.97(3.80)	5.28(1.24)						
Old	15.50(2.62)	8.22(1.92)						
Efficiency (%)			20.21	27.91	0.40	<0.001	<0.001	0.538
Young	92.95(1.17)	97.68(0.39)						
Old	84.62(2.17)	90.63(1.30)						
WASO (%)			21.46	27.27	0.63	<0.001	<0.001	0.440
Young	5.54(1.06)	1.07(0.33)						
Old	14.43(2.25)	8.36(1.35)						
Stage 2 (%)			3.86	0.283	7.92	0.067	0.602	0.012
Young	54.59(1.30)	50.37(2.19)						
Old	57.34(2.92)	60.22(2.96)						
SWS (%)			24.88	40.63	6.39	<0.001	<0.001	0.022
Young	11.90(1.16)	19.50(1.76)						
Old	2.75(1.09)	6.03(2.48)						
REM (%)			1.21	0.48	0.39	0.288	0.497	0.540
Young	25.74(1.21)	27.69(2.22)						
Old	23.34(2.58)	23.44(3.09)						

Note: Values are expressed as Mean(SEM). PSG = polysomnography, TST = total sleep time, Latency = time to first stage 2 epoch, efficiency = sleep efficiency, WASO = wake after sleep onset, Stage 2 = stage 2 sleep, SWS = slow wave sleep, REM = rapid eye movement sleep, Baseline = average of night two for both visits, SR = Sleep Recovery following sleep deprivation, A = Age, C = Sleep Condition.

Spectral Data

Following sleep deprivation, spectral properties changed at multiple frequencies. These changes were observed in delta, theta, alpha, and sigma frequency ranges. The current analysis is limited to delta and sigma frequencies, the frequencies of slow waves and sleep spindles, two prominent features of NREM sleep.

Delta Power

Sleep deprivation resulted in an increase in delta power in both age groups, particularly in the first half of the night, Figure 3.1. This effect was greater in young than old adults. At C3, a main effect of age group, hour, and condition were detected, as were age group by hour, age group by condition, condition by hour, and age group by condition by hour interaction effects (For "Age Group", $F_{1,7,16} = 12.149$, $p = 0.003$; for "Sleep Condition", $F_{1,7,16} = 21.523$, $p < 0.001$; for "Hour", $F_{1,7,16} = 26.22$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,7,16} = 4.308$, $p = 0.054$; for "Age Group × Hour", $F_{1,7,16} = 8.47$, $p < 0.001$; for "Sleep Condition × Hour", $F_{1,7,16} = 9.494$, $p < 0.001$; for "Age Group × Sleep Condition × Hour", $F_{1,7,16} = 5.33$, $p < 0.001$). This effect was similar at C4 (For "Age Group", $F_{1,7,16} = 13.226$, $p = 0.002$; for "Sleep Condition", $F_{1,7,16} = 22.237$, $p < 0.001$; for "Hour", $F_{1,7,16} = 26.439$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,7,16} = 5.03$, $p = 0.039$; for "Age Group × Hour", $F_{1,7,16} = 8.757$, $p < 0.001$; for "Sleep Condition × Hour", $F_{1,7,16} = 10.249$, $p < 0.001$; for "Age Group × Sleep Condition × Hour", $F_{1,7,16} = 5.607$, $p < 0.001$). Of note was the presence of an age difference in both conditions, whereby young adults had a greater C4-C3 delta power difference than old

adults (for "Age Group", $F_{1,7,16} = 5.364$, $p = 0.034$) which tended to decrease across the night (for "Hour", $F_{1,7,16} = 1.796$, $p = 0.095$). This effect did not differ by condition and reflects a modestly greater delta power in the right hemisphere of young adults, which disappears with age.

In order to examine the 'dissipation of the homeostatic drive for sleep', hourly means were logarithmically transformed and slopes were fitted. For both young and old adults, delta power peaked early in the night and decreased exponentially across the night. Slopes of delta power were steeper for recovery sleep in both age groups, and there was no age difference in either condition despite having drastically different levels of overall delta power (For "Age Group", $F_{1,16} = 1.018$, $p = 0.328$; for "Sleep Condition", $F_{1,16} = 13.934$, $p = 0.002$; for "Age Group × Sleep Condition", $F_{1,16} = 2.44$, $p = 0.138$; -0.19±0.02 for SO, -0.26±0.02 for SR (Young); -0.19±0.02 for SO, -0.22±0.02 for SR (Old), Figure 3.2).

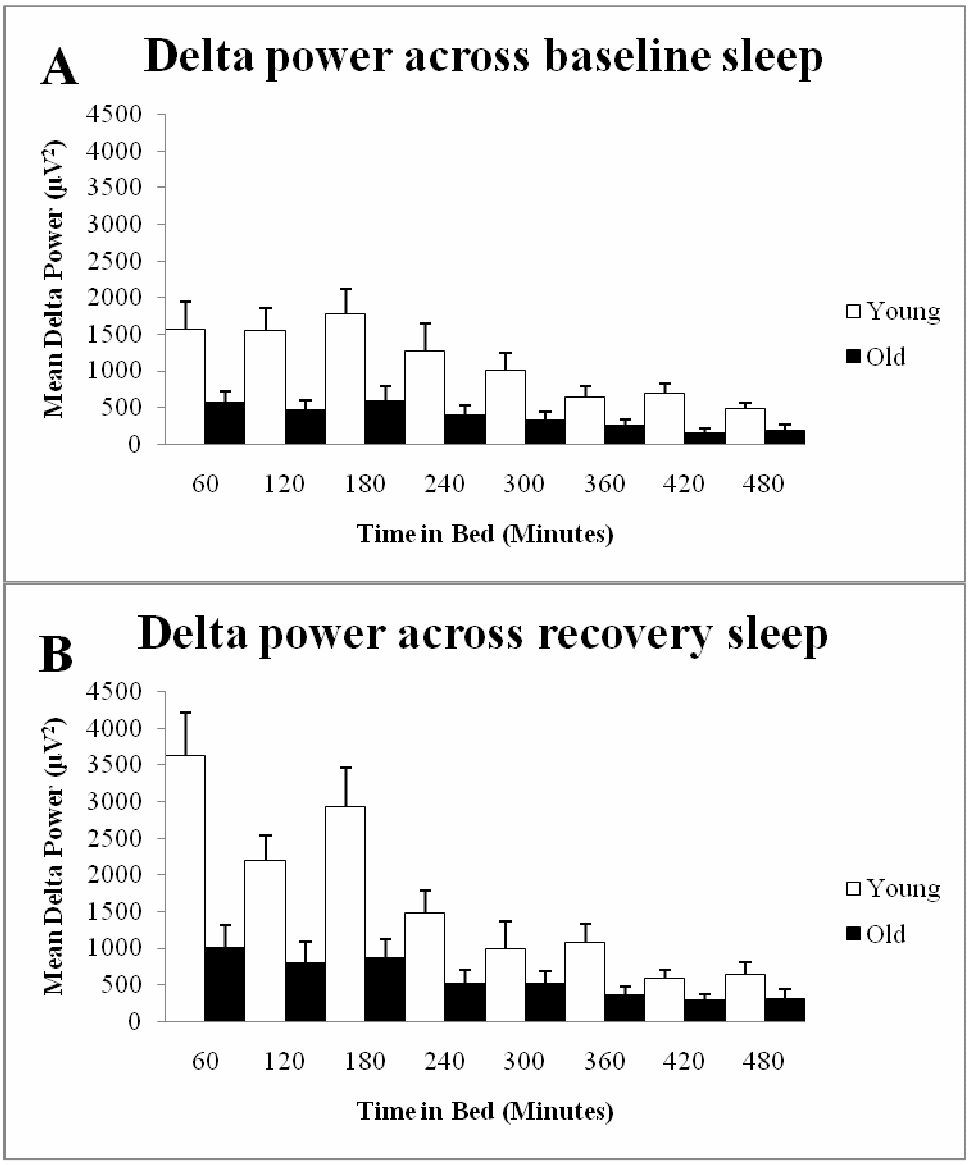

Figure 3.1. Spectral power (μV^2) in the delta frequency range (0.5-4.5 Hz) at C3. Spectral power is plotted across the night in 60 minute bins for both young (white) and old (black) adults for baseline **(a)** and recovery **(b)** nights. Values are presented as mean±sem.

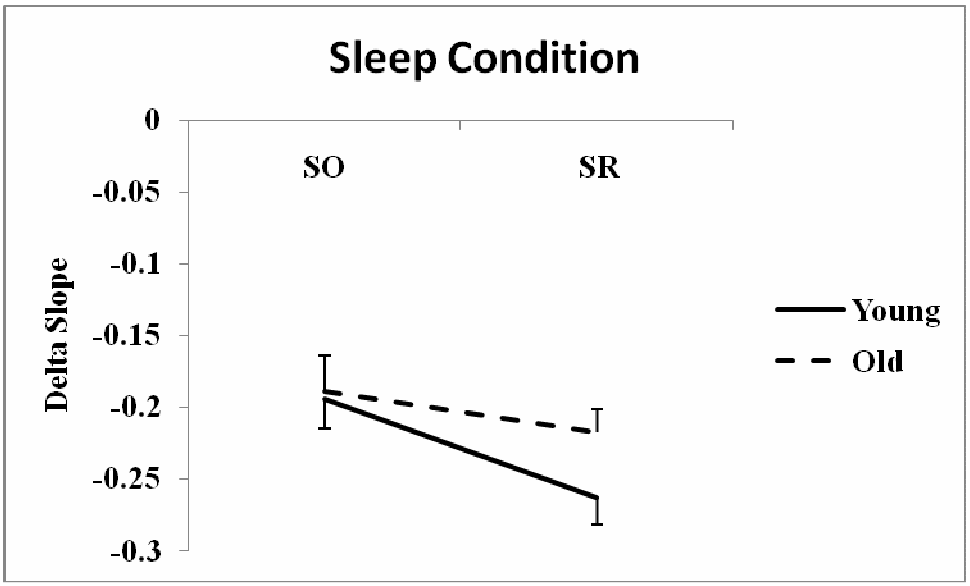

Figure 3.2. Slope of delta power at C3 in baseline (SO) and recovery (SR) conditions in young (solid line) and old (dashed line) adults. Values are presented as mean±sem.

Sigma Power

Sleep deprivation resulted in an increase in sigma power in young adults, particularly in the second half of the night, Figure 3.3. At C3, a main effect of age group and condition were detected, as were age group by hour, condition by hour, and age group by condition by hour interaction effects (For "Age Group", $F_{1,7,16} = 6.611$, $p = 0.021$; for "Sleep Condition", $F_{1,7,16} = 0.065$, $p = 0.803$; for "Hour", $F_{1,7,16} = 7.057$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,7,16} = 0.07$, $p = 0.794$; for "Age Group × Hour", $F_{1,7,16} = 5.972$, $p < 0.001$; for "Sleep Condition × Hour", $F_{1,7,16} = 2.738$, $p = 0.012$; for "Age × Group Sleep Condition × Hour", $F_{1,7,16} = 2.086$, $p = 0.051$). This effect was similar at C4 (For "Age Group", $F_{1,7,16} = 7.393$, $p = 0.015$; for "Sleep Condition", $F_{1,7,16} = 0.347$, $p = 0.564$; for "Hour", $F_{1,7,16} = 7.986$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,7,16} = 1.015$, $p = 0.329$; for "Age Group × Hour", $F_{1,7,16} = 5.865$, $p < 0.001$; for "Sleep Condition × Hour", $F_{1,7,16} = 2.198$, $p = 0.040$; for "Age Group × Sleep Condition × Hour", $F_{1,7,16} = 1.991$, $p = 0.062$).

In order to examine the buildup of sigma power across the night, hourly means were logarithmically transformed and slopes were fitted. Slopes of sigma power were steeper for recovery sleep in both age groups, and sigma power was higher in both conditions for young adults (For "Age Group", $F_{1,16} = 19.895$, $p < 0.001$; for "Sleep Condition", $F_{1,16} = 20.687$, $p < 0.001$; for "Age Group × Sleep Condition", $F_{1,16} = 1.564$, $p = 0.229$; 0.032 ± 0.01 for SO, 0.067 ± 0.01 for SR (Young); -0.012 ± 0.01 for SO, 0.007 ± 0.01 for SR (Old), Figure 3.4).

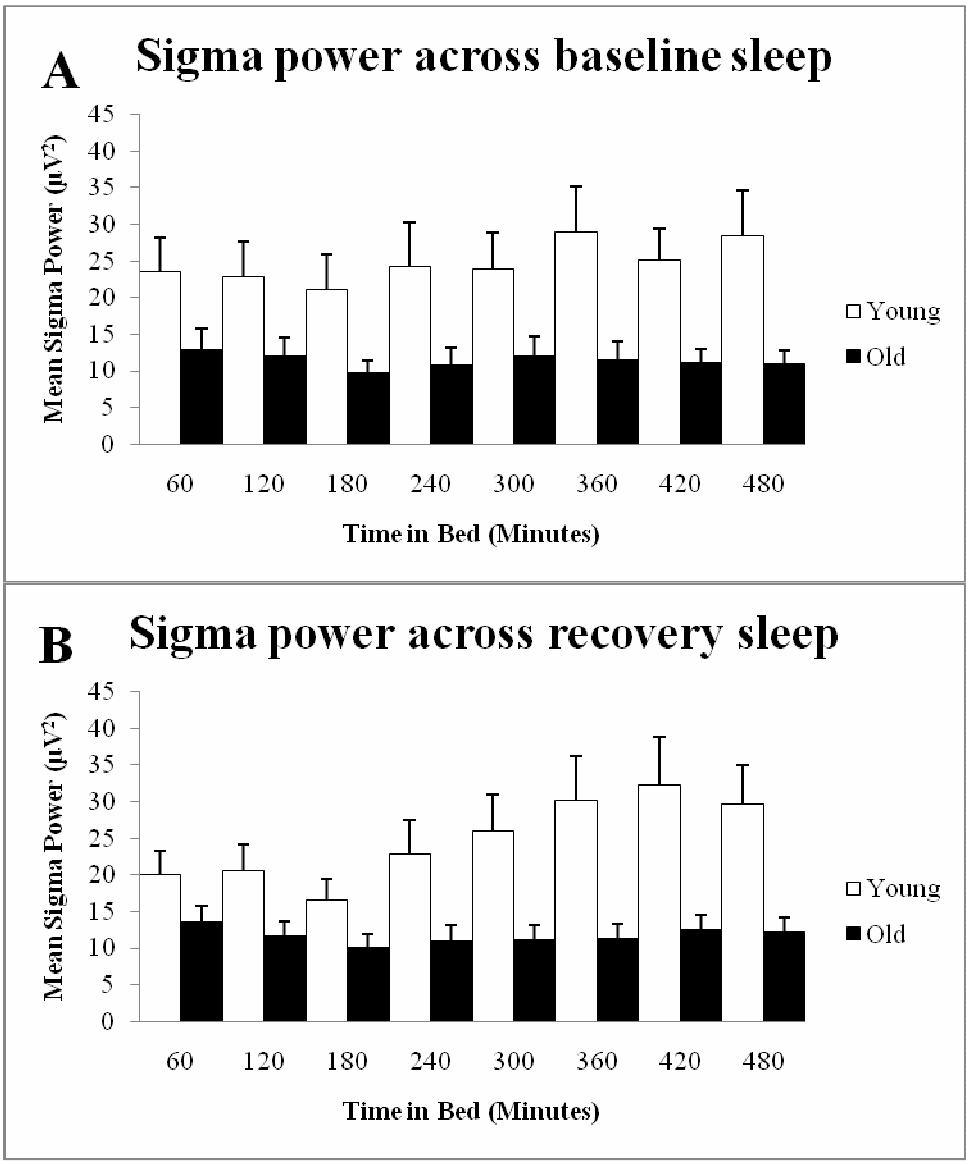

Figure 3.3. Spectral power (μV^2) in the sigma frequency range (12.5-15.5 Hz) at C3. Spectral power is plotted across the night in 60 minute bins for both young (white) and old (black) adults for baseline **(a)** and recovery **(b)** nights. Values are presented as mean±sem.

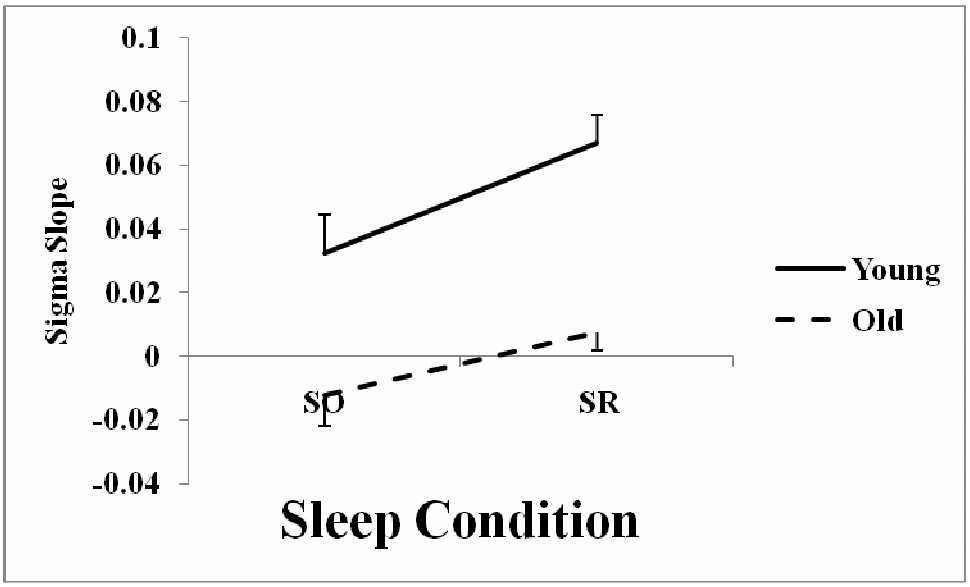

Figure 3.4. Slope of sigma power at C3 in baseline (SO) and recovery (SR) conditions in young (solid line) and old (dashed line) adults. Values are presented as mean±sem.

Behavioral Data

Recovery from sleep deprivation resulted in a near return to baseline in young and old adults on go/no-go task performance. A metric of errors of omission, percent of correct responses, was examined in both age groups and sleep conditions. A main effect of age group relating to percentage of correct responses (targets) was detected with young adults responding correctly more often than old adults (For "Age Group", $F_{1,16} = 5.230$, $p = 0.036$; for "Sleep Condition", $F_{1,16} = 0.284$, $p = 0.601$; for "Age Group × Sleep Condition", $F_{1,16} = 2.485$, $p = 0.135$; Young 97.5%±1.6% to 94.4%±2.2%; Old 82.3%±6.6% to 88.5%±2.9%, Figure 3.5A).

Percent of correct inhibitions was examined as a measure of inhibitory performance in both age groups and sleep conditions. Overall mean performance did not differ between sleep opportunity (SO) and sleep recovery (SR) conditions. There was a trend for a main effect of sleep condition, but no age group or age by sleep condition interaction was detected (For "Age Group", $F_{1,16} = 0.536$, $p = 0.475$; for "Sleep Condition", $F_{1,16} = 4.085$, $p = 0.060$; for "Age Group × Sleep Condition", $F_{1,16} = 0.003$, $p = 0.958$, Figure 3.5B). Both age groups appear to show a slight decrease in percent of correct inhibitions from the sleep opportunity to the sleep recovery condition (Young 92.6%±1.9% to 89.6%±3.2%; Old 90.5%±1.7% to 87.6%±2.1%).

In order to examine the effects of age on the ability to recover from sleep deprivation in terms of overall performance accuracy, a measure of response bias, d', was calculated from the proportions of correct responses, correct inhibitions, misses (errors of omission), and false alarms (errors of commission) (Green & Swets, 1966). A main

effect of age relating to performance accuracy was detected (For "Age Group", $F_{1,16}$ = 7.738, p = 0.013; for "Sleep Condition", $F_{1,16}$ = 2.379, p = 0.143; for "Age Group × Sleep Condition", $F_{1,16}$ = 2.264, p = 0.152, Figure 3.5C). Young adults responded significantly more often and more accurately than old adults. However, both groups were similar in terms of commission errors, and both showed a trend towards worse inhibitory performance even after a night to recover from sleep deprivation.

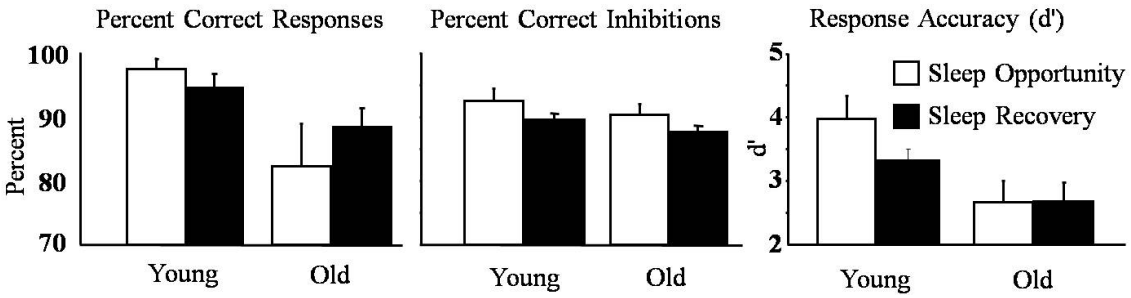

Figure 3.5. Go/No-Go task performance by age and sleep condition. Percentage of correct responses **(a)** and correct inhibitions **(b)** after a night of nine hours of sleep opportunity (white) and after a night of ten hours of sleep opportunity to recover from sleep deprivation (black) is presented for young and old adults. Response accuracy metric d' **(c)** after a night of nine hours of sleep opportunity (white) and a night of ten hours of sleep opportunity to recover from of sleep deprivation (black) is presented for young and old adults.

MRI Data

Activity within prefrontal regions associated with inhibitory control and affected by sleep deprivation were examined by extracting contrast estimates within predetermined volumes of interest (VOIs) using the MarsBaR toolbox within SPM5 ((Brett et al., 2002), see General Methods: fMRI analysis, 'Chapter 3: Age alters neural responses associated with recovery from sleep deprivation within the prefrontal cortex'). BOLD responses to no-go events were compared to BOLD responses to go events as previously reported ((Booth et al., 2003), see General Methods: fMRI analysis, 'Chapter 2: Age alters the neural response to sleep deprivation within frontal cortex'). Responses within the right prefrontal cortex VOIs 2 and 3 were reduced even after sleep recovery (VOI-1: For "Age Group", $F_{1,16} = 4.874$, $p = 0.042$; for "Sleep Condition", $F_{1,16} = 1.101$, $p = 0.310$; for "Age Group × Sleep Condition", $F_{1,16} = 0.381$, $p = 0.546$; VOI-2: For "Age Group", $F_{1,16} = 11.479$, $p = 0.004$; for "Sleep Condition", $F_{1,16} = 8.270$, $p = 0.011$; for "Age Group × Sleep Condition", $F_{1,16} = 2.352$, $p = 0.145$; VOI-3: For "Age Group", $F_{1,16} = 0.583$, $p = 0.456$; for "Sleep Condition", $F_{1,16} = 5.223$, $p = 0.036$; for "Age Group × Sleep Condition", $F_{1,16} = 1.821$, $p = 0.196$, Figure 3.6A-C). Though there were no significant age by sleep condition interactions, reductions appear largest in the old adults. Main effects of age were detected in VOIs 1 and 2, with old adults showing lower right prefrontal activation in all conditions. A significant age by sleep condition interaction was detected in the left prefrontal cortex with old adults showing reduced activity and young adults showing a persistant increase in activity (For "Age Group", $F_{1,16} = 3.528$, $p = 0.079$; for "Sleep Condition", $F_{1,16} = 0.896$, $p = 0.358$; for "Age Group × Sleep

Condition", $F_{1,16} = 4.658$, $p = 0.046$, Figure 3.6D). However, this was probably due to the fact that older adults showed higher left prefrontal cortex recruitment during inhibitory events in the sleep opportunity, which decreased after sleep deprivation (Old *versus* Young, SO condition, I-T Contrast: $t = -2.948$, $p = 0.009$).

Activation associated with correct inhibitions (I-T contrast) within each right prefrontal VOI was regressed against the percent of correct inhibitions in the SO condition. A significant negative association was detected in VOI-2 in young adults ($F = 5.461$, $r = 0.662$, $p = 0.052$), and a positive trend was detected in VOI-2 in old adults ($F = 4.093$, $r = 0.607$, $p = 0.083$, Figure 3.7). This baseline difference in the relationship between brain activity and performance is reminiscent of the data of Rympa and D'Esposito (Rypma & D'Esposito, 2000), suggesting that right prefrontal activation relates to inhibitory performance differentially in young and old adults. Specifically, when old adults have high activation, inhibitory performance is best, whereas when young adults have high activation, errors of commission are more likely to occur.

When examining relationships between changes in right prefrontal activation from SO to SR conditions and inhibitory performance change from SO to SR conditions, all three right prefrontal VOIs showed a negative relationship for young adults (VOI-1: $F = 6.828$, $r = 0.703$, $p = 0.035$; VOI-2: $F = 41.998$, $r = 0.926$, $p < 0.001$; VOI-3: $F = 8.254$, $r = 0.736$, $p = 0.024$) and no discernable relationship for old adults (VOI-1: $F = 0.158$, $r = 0.149$, $p = 0.703$; VOI-2: $F = 2.893$, $r = 0.541$, $p = 0.133$; VOI-3: $F = 0.193$, $r = 0.164$, $p = 0.674$). This relationship was strongest in VOI-2, Figure 3.8. These data suggest that reducing activation resulted in more recovered performance. Examining the data more

closely, this relationship was driven by young adults who showed the poorest performance at baseline and the highest right prefrontal activation who then reduced activation to the optimal range in the SR condition. One subject showed high activation at baseline, poor inhibitory performance, and increased right prefrontal activation in the SR condition. This subject showed the poorest performance recovery. No other significant relationship between BOLD response and inhibitory performance was observed in the SO or SR conditions in either the right or left prefrontal cortex.

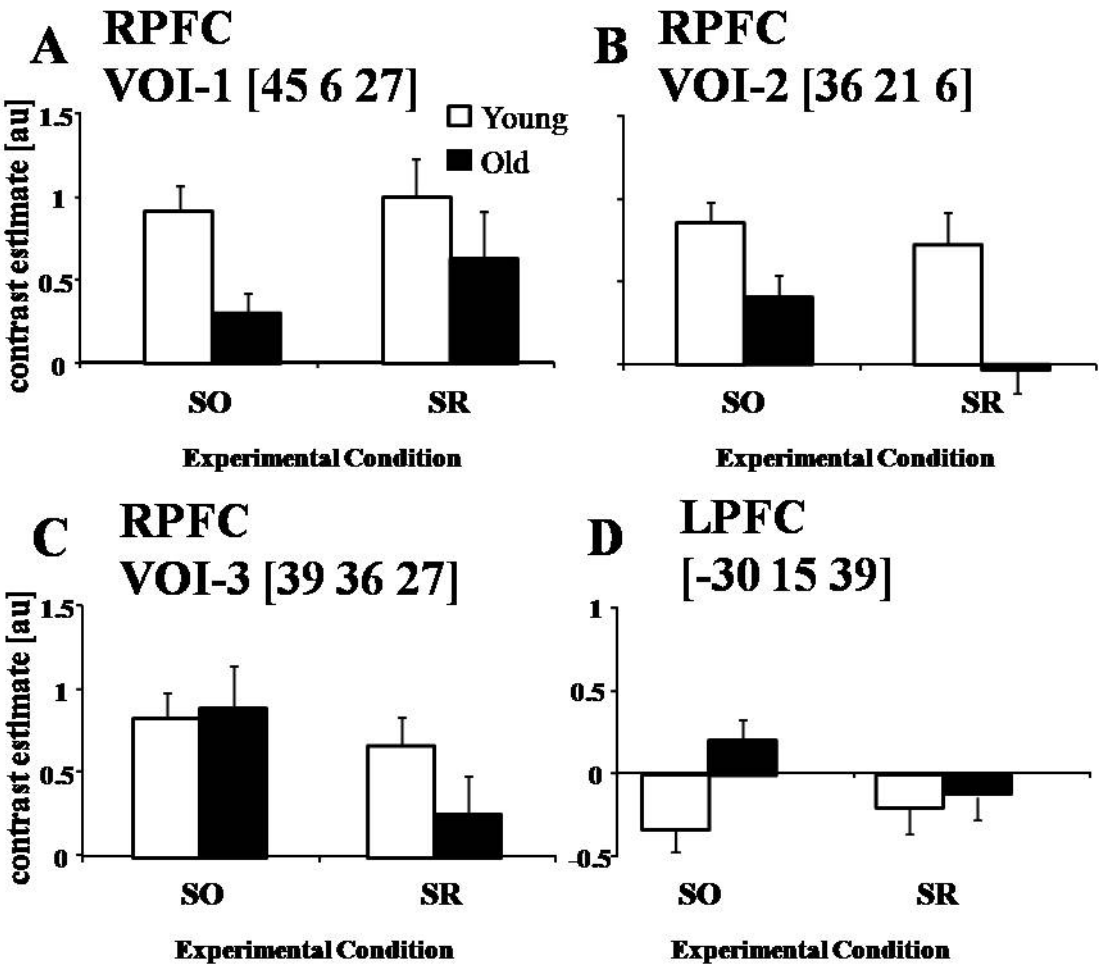

Figure 3.6. Mean activation during Sleep Opportunity (SO) condition and Sleep Recovery (SR) conditions within three right ventral lateral prefrontal cortex VOIs (**a-c**) and one left dorsal lateral prefrontal cortex VOI (**d**) during inhibitory events (correct inhibitions – targets contrast) in young (white bars) and old (black bars) adults.

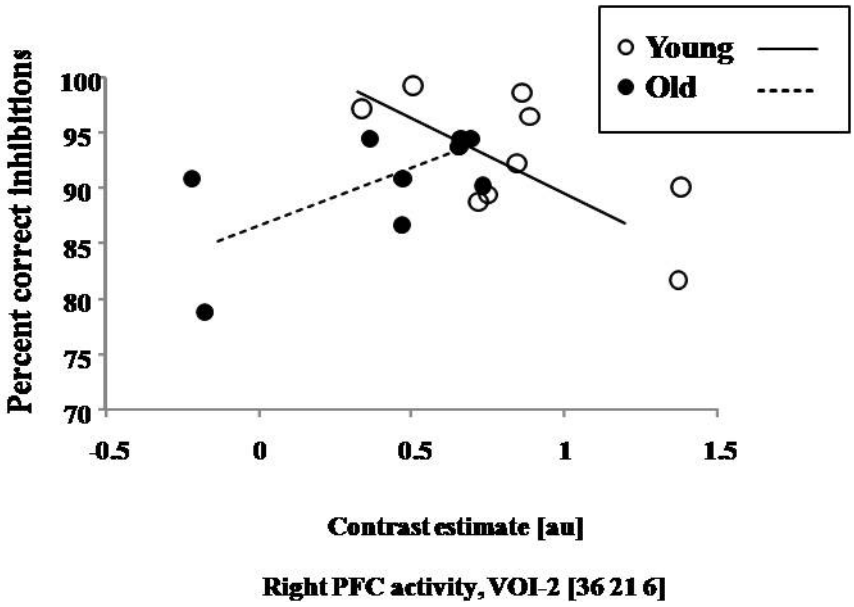

Figure 3.7. Right prefrontal activation in the SO condition at VOI 2 xyz coordinates [36 21 6] in relation to inhibitory performance in young (open circles) and old (closed circles) adults.

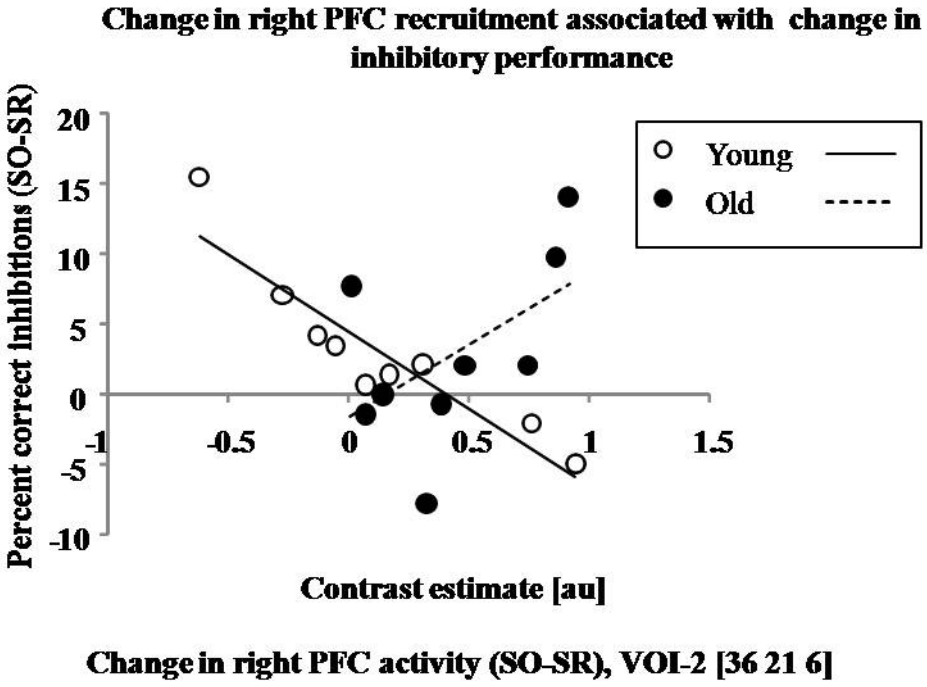

Figure 3.8. Change in right prefrontal activation from the SO condition to the SR condition regressed against inhibitory performance change at VOI-2 xyz coordinates [36 21 6] in young (open circles) and old (closed circles) adults.

Spectral power and fMRI associations

Delta power as a predictor variable

Change in early night delta power (first three hours) from baseline to recovery nights was first regressed against the change in the mean BOLD response from SO to SR conditions during inhibitions (Inhibitions – Targets contrast) within the predetermined volumes of interest in the right and left prefrontal cortex. A significant positive association was observed in the right prefrontal cortex volume of interest 2 for young (VOI-1: $F = 0.733$, $r = 0.308$, $p = 0.420$; VOI-2: $F = 6.73$, $r = 0.70$, $p = 0.036$) and a trend was observed in prefrontal cortex volume of interest 1 for old (VOI-1: $F = 5.128$, $r = 0.650$, $p = 0.058$; VOI-2: $F = 2.253$, $r = 0.493$, $p = 0.177$) adults. This suggests that the relationship between delta power and prefrontal function is altered in older adults, with young adults recovering more anterior prefrontal activation and old adults recovering more posterior prefrontal activation. No such relationship was observed with left prefrontal cortex in either age group. These data were suprising, for they suggest that those with larger increases in delta power had reduced right prefrontal recruitment the next day. Interestingly, upon closer inspection, individuals that had the highest baseline right prefrontal activation and showed the highest increases in delta power showed a reduction of right prefrontal activity towards the activation level that showed the optimal inhibitory performance in the SO condition. These individuals also showed the most recovered inhibitory performance. Individuals that had the highest baseline right prefrontal activation and showed a smaller increase in delta power showed an increase in right prefrontal activation and showed the least recovered inhibitory performance.

To examine such relationships in greater detail, change in early night delta power from baseline to recovery nights was regressed against whole brain activation change from SO to SR conditions during inhibitions (Correct Inhibitions – Targets contrast; Table 3.2). Positive correlations were detected in the left putamen and midbrain in young adults, and in the left parietal and bilateral occipital cortex in old adults. A negative association was detected in the right hippocampus in old adults.

Table 3.2: Delta power (SR-SO) versus activation (SO-SR; No-go versus Go events)

Age, Brain Region, and Contrast	r direction (+,-)	MNI Coordinates X	y	z	z score	voxel #
Young						
L putamen	+	-30	9	0	3.89	32
L midbrain	+	-6	-18	-12	4.28	55
Old						
R inferior parietal lobule	+	15	-66	57	3.60	32
R occipital cortex	+	33	-78	27	4.03	25
L occipital cortex	+	-39	-69	24	3.59	26
R hippocampus	-	30	-24	-12	4.03	25

Sigma power as a predictor variable

Change in late night sigma power (last three hours) from baseline to recovery nights was first regressed against the change in the mean BOLD response from SO to SR conditions during inhibitions (Correct Inhibitions – Targets contrast) within the predetermined volumes of interest in the right and left prefrontal cortex. A significant negative association was detected in the right prefrontal cortex VOI 2 and 3 for young (VOI-2: $F = 6.559$, $r = 0.696$, $p = 0.037$; VOI-3: $F = 26.660$, $r = 0.890$, $p = 0.001$) but not old (VOI-2: $F = 0.717$, $r = 0.305$, $p = 0.425$; VOI-3: $F = 0.207$, $r = 0.170$, $p = 0.663$) adults. These data suggest an age-related change in the way sigma results in recovered brain activity. To examine such relationships in greater detail, change in late night sigma power from baseline to recovery nights was regressed against whole brain activation change from SO to SR conditions during inhibitions (Correct Inhibitions – Targets contrast; Table 3.3). A significant negative correlation was detected within the right primary motor cortex for old adults. No significant correlations were detected in young adults.

To explore further how these spectral variables during sleep relate ultimately to performance, changes in delta and sigma percentage were regressed against inhibitory performance. For young adults, a positive association between sigma power change and performance difference was detected ($F = 12.856$, $r = 0.805$, $p = 0.009$). This relationship was not present in old adults ($F = 1.515$, $r = 0.422$, $p = 0.258$). Though this relationship did not reach significance with regards to delta power, the relationship appeared to be in

the opposite direction. Because of this relationship, and because sleep spindles and slow waves reciprocally inhibit each other, percentage change in late night sigma power was subtracted from percentage change in early night delta power (Dijk et al., 1993). This calculation gives an estimate of the relative contribution of delta versus sigma, i.e. which of these two spectral variables increases *more* following recovery sleep? This was then regressed against inhibitory performance change and right prefrontal VOI activation. Young adults showed a significant positive relationship between delta/sigma ratio and right prefrontal VOI-2 activation change ($F = 14.297$, $r = 0.819$, $p = 0.007$, Figure 3.9A), and a significant negative relationship between delta/sigma ratio and inhibitory performance change ($F = 5.954$, $r = 0.678$, $p = 0.045$, Figure 3.9B). That is to say, young individuals that had a larger increase in delta and a smaller increase in sigma during recovery sleep had better inhibitory performance recovery the next day. This is in spite of the fact that delta power increases resulted in lower right prefrontal cortex activation the next day. However, those that reduced right prefrontal activation and showed high delta power had the most recovered performance the next day. Those that showed increased right prefrontal activation and low delta power and high sigma power showed the least performance recovery the next day. These data suggest a complex relationship between slow waves, sleep spindles and neural and performance recovery, which is altered by age. Specifically, young adults who increase delta power more than sigma power showed more right prefrontal activity reduction and more performance recovery. This relationship was not observed in old adults, who instead showed relationships

between sigma changes, right primary motor activity and inhibitory performance. In both cases, sigma increases appear to hamper performance recovery.

Table 3.3: Sigma power (SR-SO) versus activation (SO-SR; No-go versus Go events)

Age, Brain Region, and Contrast	r direction (+,-)	MNI Coordinates x	y	z	z score	voxel #
Young						
No significant activations						
Old						
R primary motor cortex	-	33	-18	72	4.06	26

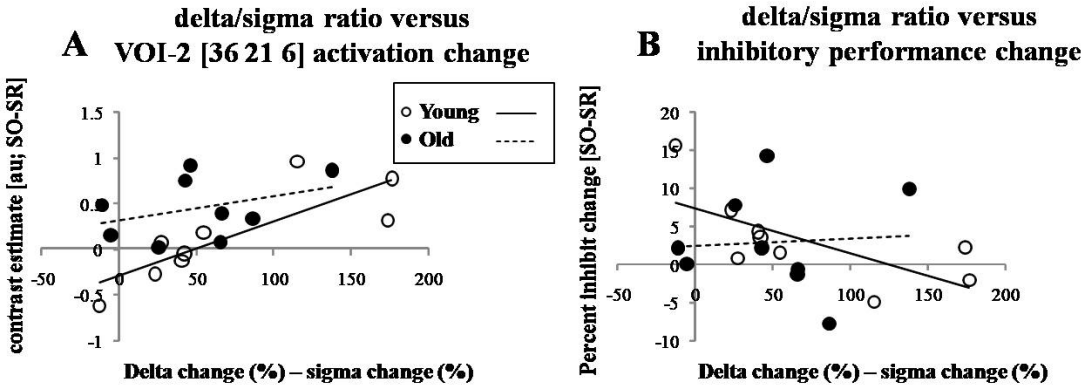

Figure 3.9. Change in delta/sigma ratio (% delta change from baseline to SR - % sigma change from baseline to SR) versus right prefrontal activation change (VOI-2; xyz coordinates [36 21 6]) from SO to SR conditions (**a**) and inhibitory performance change from SO to SR conditions (**b**) in young (open circles) and old (closed circles) adults.

Discussion

These data suggest, at least in the context of a go/no-go task, that neural responses have not returned to baseline after one night of recovery from sleep deprivation. This is true for both young and old adults, and age appears to alter this response. Specifically, young adults have increased left prefrontal cortex activation, and both age groups show decreased right prefrontal cortex activation. Change in right prefrontal cortex activation was predictive of performance recovery for young adults but not old adults. Therefore, differences in brain activation persist even after one night with ten hours of sleep opportunity to recover from sleep deprivation. Furthermore, these differences depend on age, suggesting that young and old adults may recover cognitively from sleep deprivation in different ways.

Spectral analysis of EEG data in the delta and sigma bands suggests that age-related changes exist in spectral power at both baseline and during recovery. These delta and sigma changes relate to changes in the recovery of prefrontal activation the next day. The data from chapter 2 show that sleep deprivation results in a reduction of right prefrontal cortex activation during inhibitory events in both young and old adults (see chapter 2, Figure 2.2). These data show presently that, for young adults, the recovery of inhibitory performance depends upon a greater relative increase in delta power versus sigma power the night following sleep deprivation. Delta waves originate in the prefrontal cortex and propagate as traveling waves through fronto-parietal cortex (Massimini et al., 2004). It seems reasonable to hypothesize that these delta waves somehow restore function to regions affected by sleep deprivation. Tononi has

hypothesized that slow waves act to globally downscale synaptic strengths, thus reducing metabolic burden and improving signal to noise ratio (Tononi & Cirelli, 2003, 2006). This improvement in signal to noise ratio was suggested to play a part in the role of sleep for improvement of learning and memory. If this is the case, improved signal to noise ratio would also lead to improved processing efficiency within frontal regions. This, in itself, could lead to recovered task-related brain activation the following day. Alternatively, or perhaps conjunctively, slow waves may act to reduce the effects of oxidative stress (Schulze, 2004), to which the frontal cortex is particularly sensitive (Crivello, Rosenberg, Dallal, Bielinski, & Joseph, 2005; Denisova, Shukitt-Hale, Rabin, & Joseph, 2002). These data argue that, at least in the young, slow wave sleep acts to restore next day frontal function, and the degree to which this restoration occurs depends on the capacity to increase early night delta power when challenged with sleep loss.

Old adults do not show this relationship with delta power and next day brain activity, show reduced delta power increases, and show persistent right prefrontal activation decreases. Instead, old adults appear to rely on spectral power in the sigma band, to recruit more right motor cortex activation. Sigma power is the frequency band for sleep spindles, and spindles have been shown to be important for motor learning (Walker et al., 2002). Learning a motor task has also been associated with increased right primary motor activity following sleep (Walker, Stickgold, Alsop et al., 2005). It is possible that in light of reduced dorsal prefrontal functioning and reduced delta power, old adults rely on a different strategy to perform the motor inhibition task. This strategy may depend on optimizing sensory-motor stimulus response processes in visual and

motor regions. These data suggest that not only do old adults respond to sleep deprivation differently, but rely on different EEG variables to recover from sleep deprivation which further reflects a difference in compensatory mechanisms utilized the following day.

It is important to note, however, that these brain activation and performance differences are small, especially in comparison to sleep deprivation. However, they are consistent with the changes observed after sleep deprivation. Sleep deprivation impairs inhibitory performance in both young and old adults (see chapter 2 entitled 'Age alters the neural response to sleep deprivation within frontal cortex'). In addition, young adults had increased left prefrontal cortex activation after sleep deprivation, while young and old adults showed decreased right prefrontal cortex activation. Thus, it appears these changes persist, if in a much more mild form. These changes may explain the subtle residual performance differences observed in the current report. This is consistent with a recent report which showed that within the prefrontal cortex relative changes in metabolic rate persisted after one night to recover from sleep deprivation in young adults (Wu et al., 2006).

After recovery sleep, greater left prefrontal cortex activation during inhibitions predicted better inhibitory performance in young adults. This region has been implicated in inhibitory control in previous studies (Rubia et al., 2001). The fact that recruitment of this area increases both after sleep deprivation and remains higher after sleep recovery suggests recruitment of this area is compensatory. This is further evidenced by the fact that, at least in young adults, recruitment of this area predicts better inhibitory

performance in the sleep recovery condition. Old adults do not show this relationship, and even show highest left prefrontal recruitment after normal sleep opportunity. It may be that old adults are already stressed by age, and thus are already using compensatory mechanisms. When sleep deprivation is added, perhaps their ability to recruit compensatory mechanisms is impaired. However, left prefrontal activity did not predict good performance after normal sleep opportunity. It may be that old adults process the stress of sleep deprivation differently, or that they have reduced compensatory reserves. Further, old adults may rely on different strategies to compensate, which rely on different brain regions.

In conclusion, the neural response to recovery from sleep deprivation appears to differ with age. Relative decreases in activation were larger in old adults, and relative, compensatory increases were larger in young adults. Further, the relationship between spectral power in the delta and sigma bands during sleep and brain activation following sleep differed in young and old adults. These data suggest that age not only alters the way in which brain activation relates to performance, but also the way in which those relationships are recovered following sleep deprivation. Future studies will need to examine more closely the nature of the compensatory response within prefrontal regions such as within the dorsolateral prefrontal cortex. Response within this region in the face of sleep deprivation, at least in young adults, appears to be consistent across studies and tasks (Chee & Choo, 2004; Drummond et al., 2000; Drummond et al., 2004; Wu et al., 2006). Compensatory recruitment of this region now also appears to be present when young adults are recovering from sleep deprivation. Understanding the nature of such

compensatory mechanisms and how they change with age may yield new ways in which to manage cognitive impairments due to sleep loss.

Chapter 4: Associations between baseline brain activation and the behavioral response to sleep loss and recovery in young and old adults.

Abstract

Performance impairment following sleep deprivation is highly variable across individuals. This individual variability in the response to sleep deprivation is stable across multiple testing sessions, and is not totally explained by previous sleep history, education level, baseline performance, age, and measures of personality. Recent studies have shown that baseline parietal and frontal activation is associated with the response to sleep deprivation (Chee et al., 2006). However, it is unknown whether these effects will generalize beyond working memory tasks or across age groups. In the current study, we examined the relationship between brain activation and go/no-go performance in young and old adults following periods of nine hours of sleep opportunity, 34-36 hours of sleep deprivation, and a subsequent period of ten hours to recovery from sleep deprivation. Greater parietal activation predicted better no-go performance in young adults and better go performance in old adults. Right prefrontal activation was associated with preserved no-go performance after sleep deprivation in young adults but not in old adults. Greater left prefrontal activation was associated with better no-go performance after sleep recovery in young adults, whereas old adults who recruited more left prefrontal activation at baseline performed worse after sleep deprivation. These data suggest that old adults respond fundamentally differently to sleep deprivation and recovery than young adults.

This is likely due to the effects of age on the neural control of inhibitory performance or a change in cognitive strategy with age.

Introduction

Performance impairment following sleep deprivation is highly variable across individuals and across tasks within individuals (Frey et al., 2004; Leproult et al., 2003; Van Dongen et al., 2004; Webb & Levy, 1984; R. T. Wilkinson, 1961). This individual variability in the response to sleep deprivation is stable across repeated sessions (Van Dongen et al., 2004), and some component of this individual variability persists when previous sleep history, education level, baseline performance, age, and measures of personality are controlled (Mu et al., 2005; Van Dongen et al., 2004).

Generally, there are two main findings regarding the association between brain activation and the effects of sleep deprivation on performance. Firstly, subjects who preserve parietal recruitment and increase or preserve left prefrontal recruitment when sleep-deprived tend to perform the best (Chee & Choo, 2004; Chee et al., 2006; Drummond et al., 2000; Mu et al., 2005). Secondly, subjects who show disinhibited default mode activation tend to perform more poorly (Chee & Choo, 2004; Chee et al., 2006; Drummond, Bischoff-Grethe et al., 2005; Lim et al., 2007).

Recently, a few studies have explored the hypothesis that individual variability in brain activation observed in habitually rested conditions could be related to the inter-individual response to sleep deprivation. These studies suggest that global activation levels are higher in subjects resistant to the effects of sleep deprivation (Caldwell et al., 2005; Mu et al., 2005). These data correspond with that from Chee's group, which

showed that baseline left parietal and frontal activations were negatively correlated with performance change following sleep deprivation, suggesting these two regions may be particularly relevant when determining sleep deprivation susceptibility (Chee et al., 2006). It is important to note, however, that these studies both used working memory tasks. Thus, it may be that these activations are specific to the sleep deprivation resilience or vulnerability of a given individual's working memory processes only.

Because of this, it becomes important to examine this relationship with regard to tasks that target other cognitive domains. Further, it will be important to elucidate the effects of sleep deprivation on brain function in combination with other commonly co-morbid stressors, such as aging. These types of studies will allow us to determine whether these individual differences are dependent upon common compensatory mechanisms and vulnerabilities, or whether the above effects are specific to sleep deprivation. In the present chapter, associations between brain activation following nine hours of sleep opportunity (SO) and performance change following sleep deprivation (Sd) and subsequent sleep recovery (SR) on a go/no-go task are examined in young and old adults. Relationships between brain activation and change in activation across sleep conditions are also explored. These analyses will be able to address the question, are the effects observed in the previous studies specific to working memory processes in young adults, or are they generalizable across age groups and task type?

Results

Associations between No-go performance change and activation during No-go events

Young and old adults both showed significant associations between regional baseline brain activation during inhibitory events and inhibitory performance change from baseline. The specific locus of these relationships differed with age and sleep condition. Young adults who recruited more rostral anterior cingulate activation during the sleep opportunity condition (baseline) were more impaired after sleep deprivation and recovery, Table 4.1, Figure 4.1A-B. Young adults, who recruited more parietal resources at baseline, had better performance recovery after one night of recovery sleep, Table 4.1, Figure 4.2A-B. Old adults were more susceptible to sleep deprivation effects if they recruited more left middle frontal gyrus activation, Table 4.1, Figure 4.1C.

Activation change from baseline to sleep deprivation and recovery was associated with performance change differentially in young and old adults. In young adults, activation change from baseline to sleep deprivation that is larger within the right occipitotemporal area and right middle frontal gyrus is associated with a larger inhibitory performance decrease, Table 4.2, Figure 4.3A. Though small and a trend ($p = 0.08$), this right prefrontal activation is located within a significant cluster within the right prefrontal cortex present during inhibitions in the SO condition (see Table 2.1: A2, Figure 4.5). No such relationship was found in old adults. Curiously, a larger change in activation from baseline to sleep recovery within the left middle frontal gyrus and bilateral parahippocampal gyri was associated with a larger performance difference between the two conditions, Table 4.2, Figure 4.3B. In contrast, a larger increase in activation

following sleep recovery within bilateral inferior parietal and right premotor cortex was associated with larger decrements in inhibitory performance, Table 4.2, Figure 4.3C. This was peculiar, since greater activation within these regions at baseline predicted better performance in the recovery condition. To examine this further, individual contrast estimates were extracted from the maximal voxel in each of these parietal regions at baseline. These contrast estimates were then regressed against the contrast estimate in the same region for the SO-SR contrast. The two were highly and positively correlated, suggesting that subjects with lower parietal activation at baseline had higher increases in activation in the SR condition, whereas subjects with higher parietal activation at baseline had lower increases in the SR condition (for left inferior parietal cortex: $F_7 = 57.42$, $r = 0.944$, $p < 0.001$; for right inferior parietal cortex: $F_7 = 95.28$, $r = 0.965$, $p < 0.001$). Old adults showed better performance after sleep recovery if they recruited more right primary motor area activation than baseline, Table 4.2, Figure 4.3D.

Table 4.1: Performance change (No-go) versus baseline activation (No-go events)

Age, Brain Region, and Contrast	r direction (+,-)	MNI Coordinates x	y	z	z score	voxel #
SO-Sd vs SO activation						
Young						
rostral anterior cingulate	+	3	30	9	4.21	81
Old						
L middle frontal gyrus	+	-54	3	39	3.90	26
SO-SR vs SO activation						
Young						
rostral anterior cingulate	+	-3	45	3	3.67	27
	+	6	24	12	4.12	21#
R superior parietal lobule	-	21	-36	72	4.63	34
R inferior parietal cortex	-	33	-66	45	3.99	31
L inferior parietal cortex	-	-27	-69	60	3.98	75
Old						
No significant activations						

Trend: $p < 0.1$ corrected

Table 4.2: Performance change (No-go) versus activation change (No-go events)

Age, Brain Region, and Contrast	r direction (+,-)	MNI Coordinates x	y	z	z score	voxel #
SO-Sd perform vs SO-Sd activation						
Young						
R occipitotemporal area	+	57	-57	9	4.47	36
R middle frontal gyrus	+	39	12	30	3.71	20#
Old						
No significant activations						
SO-SR vs SO-SR activation						
Young						
L middle frontal gyrus	+	-15	51	18	4.20	28
	+	-24	48	30	4.13	21#
L parahippocampal gyrus	+	-21	-27	-24	4.38	22
R parahippocampal gyrus	+	21	-27	-24	3.65	19#
R inferior parietal cortex	-	30	-72	39	4.40	95
L inferior parietal cortex	-	-36	-60	39	4.21	143
R premotor cortex	-	9	-9	75	3.70	22#
Old						
R primary motor cortex	-	54	-15	33	4.45	33

Trend: $p < 0.1$ corrected

Associations between Go performance change and activation during Go events

Young and old adults both showed significant associations between regional baseline brain activation during target events and target performance change from baseline. In this contrast as well, the specific locus of these relationships differed with age and sleep condition. Young adults who recruited more thalamic activation during the sleep opportunity condition (baseline) were more resistant to the effects of sleep deprivation on performance, Table 4.3, Figure 4.2C. Old adults were more susceptible to sleep deprivation effects if they recruited more midline cingulate, right supplementary motor area, right fusiform, and more anterior portions of left inferior parietal activation, Table 4.3, Figure 4.1D. Poorer performance after recovery sleep was associated with right middle temporal gyrus activation. Old adults were more resistant to sleep deprivation effects if they recruited more posterior portions of inferior parietal activation bilaterally, along with posterior cingulate activation that extended into the precuneus, Table 4.3, Figure 4.2D,and F. In addition, right superior frontal and medial frontal gyrus activation were associated with resistance to sleep deprivation as well, Table 4.3, Figure 4.2E-F. Old adults who recruited more thalamic activation at baseline had better performance after recovery sleep, Table 4.3.

Activation change from baseline to sleep deprivation and recovery was associated with performance change differentially in young and old adults. In young adults, activation change from baseline to sleep deprivation that is larger within the left inferior parietal lobule is associated with larger target performance change, Table 4.4, Figure 4.4A. In contrast, a smaller activation change from baseline to sleep deprivation within

the left inferior parietal lobule and dorsal anterior cingulate is associated with a larger target performance change in old adults, Table 4.4, Figure 4.4B. Closer examination of the contrast estimates within the most significant voxel in left parietal cortex revealed that young adults had a positive mean SO-Sd contrast difference (0.04±0.19), whereas old adults had a negative mean SO-Sd contrast difference (-0.40±0.31). This suggests that where young adults showed reduced parietal activation after sleep deprivation, old adults showed increased activation after sleep deprivation. Thus, if young adults reduced parietal activation from baseline, performance was impaired, whereas if old adults increased activation from baseline, performance was impaired. Larger performance change from baseline to sleep recovery is associated with larger activation changes within bilateral fusiform gyri and the right posterior insula, Table 4.4. Smaller performance change is associated with larger activation change within the right superior frontal gyrus, Table 4.4.

Table 4.3: Performance change (Go) versus baseline activation (Go events)

Age, Brain Region, and contrast	r direction (+,-)	MNI Coordinates x	y	z	z score	voxel #
SO-Sd vs SO activation						
Young						
R Thalamus	-	12	0	0	4.18	28
Old						
midline cingulate	+	12	-3	60	4.64	404
R supplementary motor area	+	48	-3	24	4.62	196
L inferior parietal lobule	+	-42	-36	54	4.14	89
R fusiform gyrus	+	42	-60	-21	3.65	23#
R inferior parietal lobule	-	45	-75	33	4.80	86
L inferior parietal lobule	-	-48	-75	33	4.31	56
R superior frontal gyrus	-	24	24	51	4.58	99
posterior cingulate/precuneus	-	-6	-60	27	4.56	486
R medial frontal gyrus	-	3	63	15	3.74	86
SO-SR vs SO activation						
Young						
No significant activations						
Old						
R middle temporal gyrus	+	57	-39	-12	4.05	35
L Thalamus	-	-6	-24	9	4.08	24#

Trend: $p < 0.1$ corrected

Table 4.4: Performance change (Go) versus activation change (Go events)

Age, Brain Region, and Contrast	r direction (+,-)	MNI Coordinates x	Y	z	z score	voxel #
SO-Sd perform vs SO-Sd activation						
Young						
L inferior parietal lobule	+	-51	-63	36	4.35	32
Old						
L inferior parietal lobule	-	-54	-51	42	4.08	43
dorsal anterior cingulate	-	0	21	42	3.99	49
SO-SR vs SO-SR activation						
Young						
No significant activations						
Old						
R posterior insula	+	42	-9	18	4.42	41
L fusiform	+	-36	-60	-9	4.04	35
R fusiform	+	27	-66	-12	3.74	40
R premotor area	-	45	15	45	4.66	28#

Trend: $p < 0.1$ corrected

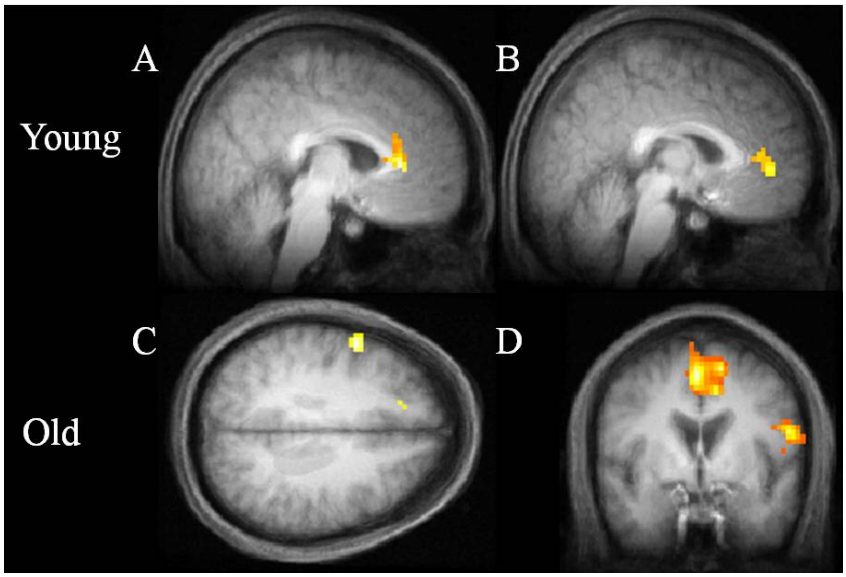

Figure 4.1. Neural correlates of sleep loss susceptibility. Baseline activation during no-go **(a-c)** and go **(d)** events related to poorer performance following sleep deprivation **(a,c-d)** and recovery **(b)** in young **(a-b)** and old **(c-d)** adults. Increased baseline activation within rostral anterior cingulate cortex during no-go events in young adults relates to poorer performance following sleep deprivation **(a)** and recovery **(b)**. Increased baseline activation within left middle frontal gyrus during no-go events in old adults relates to poorer performance following sleep deprivation **(c)**. Increased baseline activation within right supplementary motor area and midline cingulate cortex during go events relates to poorer performance following sleep deprivation **(d)**. All peaks are significant at $p < 0.05$ corrected across the entire brain volume at the cluster level.

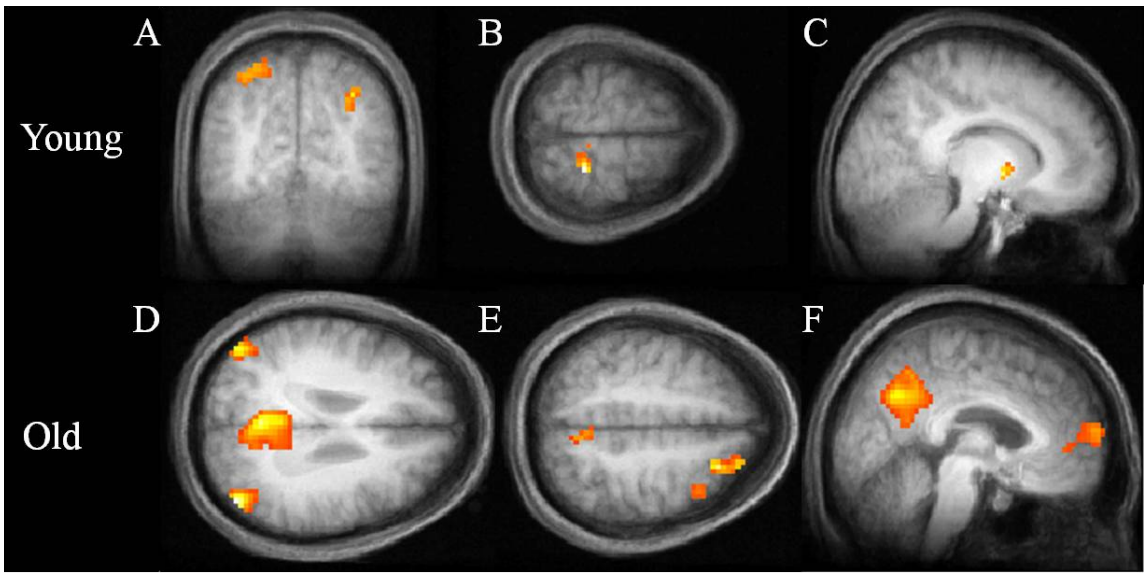

Figure 4.2. Neural correlates of sleep loss resiliency. Baseline activation during no-go **(a-b)** and go **(c-f)** events related to preserved performance following sleep deprivation **(c-f)** and recovery **(a-b)** in young **(a-c)** and old **(d-f)** adults. Increased baseline activation within bilateral parietal regions during no-go events in young adults relates to recovered performance following sleep recovery **(a-b)**. Increased baseline activation within the thalamus go events in young adults relates to preserved performance following sleep deprivation **(c)**. Increased baseline activation within bilateral parietal regions **(d)**, posterior cingulate cortex **(d,f)**, right superior and medial frontal gyri **(e-f)** during go events in old adults related to preserved performance following sleep deprivation. All peaks are significant at $p < 0.05$ corrected across the entire brain volume at the cluster level.

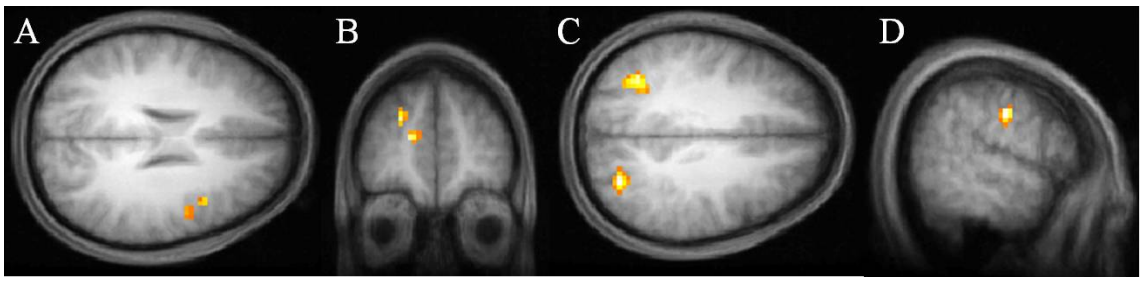

Figure 4.3. Neural correlates of inhibitory performance change following sleep loss and recovery. Change in activation from sleep opportunity (SO) to sleep deprivation (Sd) **(a)** and sleep recovery (SR) **(b-d)** conditions during no-go events related to preserved **(a-b)** and worsened **(c-d)** performance in young **(a-c)** and old **(d)** adults. Greater decreased right middle frontal gyrus activation following Sd was associated with worsened performance in young adults **(a)**. Greater decreased left middle frontal gyrus activation following SR was associated with worsened performance in young adults **(b)**. Increased parietal activation in the SR condition within bilateral parietal regions relates to worsened performance **(c)**. Increased activation in the SR condition within the right premotor cortex in old adults relates to worsened performance following sleep recovery **(d)**. All peaks are significant at $p < 0.05$ corrected across the entire brain volume at the cluster level, except the right middle frontal gyrus activation **(a)**, which is a trend at $p = 0.08$ corrected across the entire brain volume at the cluster level.

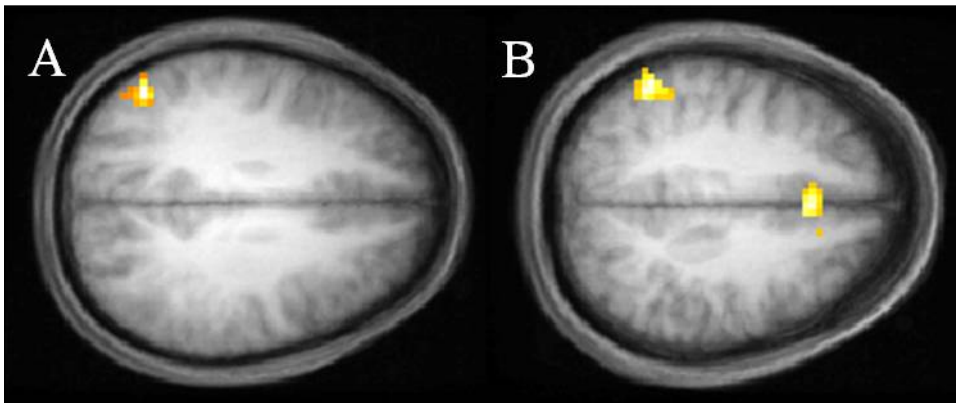

Figure 4.4. Neural correlates of go performance change following sleep loss and recovery. Change in activation from sleep opportunity (SO) to the sleep deprivation (Sd) condition during go events related to preserved **(a)** and worsened **(b)** performance in young **(a)** and old **(b)** adults. Greater decreased left inferior parietal cortex activation following Sd was associated with worsened performance in young adults **(a)**. Greater increased left inferior parietal cortex and dorsal anterior cingulate activation following Sd was associated with worsened performance in old adults **(b)**. All peaks are significant at $p < 0.05$ corrected across the entire brain volume at the cluster level.

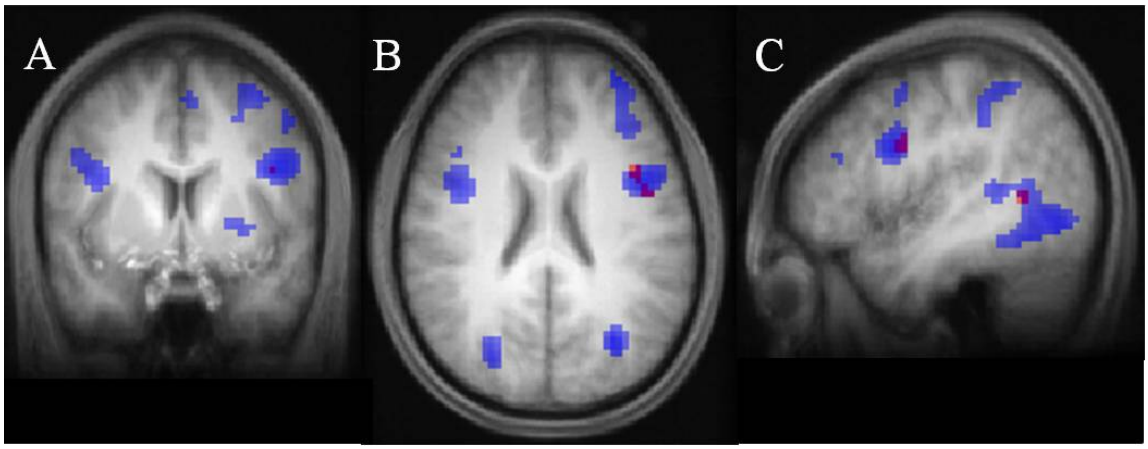

Figure 4.5. Activations from young adults during inhibitions in the SO condition (blue) are overlaid with activation change from SO to Sd that is associated positively with inhibitory performance change from SO to Sd (red). Greater decreased right middle frontal gyrus activation following Sd was associated with worsened performance in young adults **(a-c)**. Note the activation within the occipitotemporal area **(c)**, which also overlaps with a significant cluster recruited during inhibitions in the SO condition.

Discussion

These data demonstrate that the relationship between performance and both baseline regional brain activation and regional activation change across sleep conditions depends on the age of the individual and the cognitive event in question. That is to say, activations that were associated with Go/No-go performance change across sleep condition were distinct for Go and No-go events, and these associations differed in young and old adults. These data suggest that cognitive resources may be differentially utilized in young and old adults, and that because of this difference, the manner in which individual differences affect performance may differ with age. For example, in opposition to young adults, an older adult that can utilize more parietal resources may not be able to preserve no-go performance but will preserve go performance. Indeed, in terms of number of significant regional associations, there appears to be more of an emphasis on no-go performance in young adults and go performance in old adults. This may reflect differing cognitive strategies employed by young and old adults to maintain good performance, or may reflect age-related functional reorganization of neural resources (Backman et al., 1997; Cabeza, 2002; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Nielson et al., 2002; Reuter-Lorenz et al., 2000).

Similar to previous studies, greater utilization of parietal resources at baseline was associated with better performance after sleep deprivation and recovery in young and old adults (Chee et al., 2006; Mu et al., 2005). Interestingly, as stated above, *how* parietal

recruitment aided performance was dependent on age. In young adults, parietal recruitment at baseline was associated with better no-go performance recovery following a night of sleep to recover from sleep deprivation. Further recruitment within these regions above that observed at baseline resulted in worsened performance. However, those who increased parietal recruitment the most in the recovery condition were also those who had the least parietal activation at baseline. In old adults, fronto-parietal recruitment at baseline, particularly right frontal and posterior parietal recruitment, was associated with better go performance after sleep deprivation. The role of parietal activation in inhibitory processes has received little attention. This is in spite of the fact that most studies of inhibition show parietal recruitment (Bellgrove et al., 2004; Buchsbaum, Greer, Chang, & Berman, 2005; de Zubicaray et al., 2000; Garavan et al., 2002; Garavan et al., 1999; R. L. Hester et al., 2004; Rubia et al., 2001; Simmonds, Pekar, & Mostofsky, 2008), which can still be observed after accounting for some of the effects of working memory and attentional processing (Horn et al., 2003; Watanabe et al., 2002). However, as Maguire and colleagues have shown, increased activation in parietal regions can be due to a heightened spatial attention demand for correct execution of go/no-go behaviors (Maguire et al., 2003). These parietal regions provide crucial feedback to prefrontal regions, particularly when stimulus driven and goal driven attentional behaviors are executed (Corbetta & Shulman, 2002). Inferior parietal regions are known to contain a map of stimulus saliency (Gottlieb et al., 1998). It has been argued that these parietal regions maintain stimulus-response associations which prime attention towards a particular motor output (R. Hester, D'Esposito, Cole, & Garavan,

2007; Rubia et al., 2001; Simmonds et al., 2008). Thus, task rules can inform parietal regions via prefrontal input in order to form stimulus-response associations. Then, upon detection of a given stimulus, parietal regions can inform the prefrontal regions of the stimulus presented and prime the correct motor response by focusing attention upon it. This implies that more difficult behaviors, such as inhibiting prepotent responses, may benefit from more parietal input. Thus, it may not be surprising young adults who utilize more parietal resources at baseline perform better in terms of no-go performance, while old adults who utilize more parietal resources at baseline perform better in terms of go performance. As presented in chapter 2, young adults tend to make more commission errors, and old adults tend to make more omission errors. This hints at a different cognitive strategy employed by the two age groups, and also suggests that the ability to utilize more fronto-parietal resources may protect against the errors that the two age groups are more sensitive to, i.e. these resources aid in attending to the cognitive control of motor actions in general and do not specifically aid in inhibitory or selection processes per se. That is to say, these parietal resources may aid in attending to the decision to act or not act, rather than aiding in acting or not acting.

Parietal recruitment across sleep conditions was associated with performance change differentially in young and old adults. Specifically, target performance change is positively correlated with left parietal activation in young adults and negatively correlated with left parietal activation in old adults. Previous studies of working memory and attention have shown that preservation of parietal activation is associated with preserved performance (Chee & Choo, 2004; Chee et al., 2006; Drummond et al., 2000;

Mu et al., 2005). Thus, one would expect that old and young adults alike would benefit from parietal activation in this case. However, Nielson and colleagues have shown that while old adults perform a similar go/no-go task, those with the largest amount of activation were generally those who performed most poorly (Nielson et al., 2002). Upon closer examination of the data, contrast estimates of the difference in parietal activation across sleep conditions revealed that young adults were generally met with reduced parietal activation following sleep deprivation. In contrast, old adults generally increased parietal activation above baseline. Thus, where baseline levels of activation may relate to good performance, increased parietal activation above baseline may be detrimental to performance. This is reminiscent of the age-related shift on the performance-activation curve, as suggested by Rypma and colleagues (Rypma & D'Esposito, 2000).

Previous studies have suggested that increased default mode activation following sleep deprivation or aging results in larger performance impairments (Chee & Choo, 2004; Chee et al., 2006; Drummond, Bischoff-Grethe et al., 2005; Grady et al., 2006; Lim et al., 2007; Persson et al., 2007). In the current report, we found that young adults who have larger rostral anterior cingulate activation at baseline were hit hardest by sleep deprivation and recovered from it more poorly in terms of inhibitory performance. Though more anterior and ventral in nature, it is also similar to the finding by Garavan and colleagues which showed that subjects relying more on anterior cingulate activation over dorsolateral prefrontal cortex activation to inhibit prepotent responses were more prone to cognitive failures (Garavan et al., 2002). Thus, individuals more reliant on

cingulate activation may be more distractible and thus more prone to the stress of sleep loss.

Prefrontal activation was also associated with performance change following sleep loss and recovery. Predominant in the literature is the critical importance of right lateral prefrontal regions (both ventral and dorsal) for inhibitory performance (Bellgrove et al., 2004; Booth et al., 2003; Buchsbaum et al., 2005; Garavan et al., 2002; Garavan et al., 1999; Horn et al., 2003; Rubia et al., 2001; Simmonds et al., 2008; Watanabe et al., 2002). Left prefrontal recruitment has also been observed, though right prefrontal recruitment is usually dominant for motor inhibition paradigms (Bellgrove et al., 2004; Booth et al., 2003; Horn et al., 2003; Rubia et al., 2001; Watanabe et al., 2002). Lesions in these prefrontal sites result in executive impairment, particularly the presence of motor perseveration (Aron et al., 2004; Luria, 1965; Mesulam, 1986). In young adults, following sleep deprivation, a greater reduction in right middle frontal gyrus activation was associated with greater inhibitory impairments. Of note is that this cluster of right middle frontal gyrus activity overlaps almost entirely with a cluster of activity observed at normal rest using the inhibitions-targets contrast (See Table 2.1: A2 and Figure 4.5).

Following sleep recovery, a similar relationship was found in the left middle frontal gyrus. In chapters 2 and 3, we show that sleep deprivation leads to a reduction in right lateral prefrontal activation, and that this is accompanied by left prefrontal recruitment which persists in the sleep recovery condition. These data suggest that loss of right prefrontal function is related to inhibitory impairments, and that left prefrontal recruitment may be compensatory. The fact that left prefrontal activation is only

associated with performance in young adults after recovery sleep suggests that this recruitment may only be helpful for mild or residual levels of sleep loss. In old adults, the degree of left prefrontal recruitment at baseline predicted the degree of inhibitory impairment following sleep loss, i.e. more activation in the left prefrontal cortex at baseline was associated with larger inhibitory impairments after sleep deprivation. Though recruitment of this region may be compensatory in young adults, it is possible that the degree of recruitment in old adults is indicative of a stressed state at baseline. That is to say, old adults with higher left prefrontal recruitment may already be using compensatory mechanisms to perform well in baseline conditions. Those older individuals may find themselves particularly vulnerable to the stress of sleep loss, as they may already be using a 'back-up' system or cognitive strategy due to the stress of aging.

Old adults also appear to utilize more motor-related activation than young adults when performing a go/no-go task. In all cases, greater activation in these regions was associated with worse performance. For inhibitory performance, the more right primary motor activation old adults utilized at baseline, the worse their performance after sleep deprivation. Further, greater increases in right primary motor activity resulted in worse inhibitory performance after sleep recovery. For target performance, the greater right supplementary motor and midline cingulate activation at baseline, the worse their performance after sleep deprivation. Further, the more their dorsal anterior cingulate activation increased during target events, the worse their target performance. Increase of right primary motor activity after sleep recovery resulted in increased lapses. This relationship between right hemispheric motor activation and right-handed go/no-go

performance suggests that old adults whom utilize right motor activations in addition to left motor activations (see chapter 2, Table 2.2 for group activations) may be more prone to making errors. An increased tendency for bilateral recruitment in old adults has been observed in many studies utilizing many different tasks (Cabeza, 2002; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Nielson et al., 2002; Reuter-Lorenz et al., 2000). Nielson and colleagues have shown that the oldest adults with the poorest performance on a go/no-go task had larger and more bilateral task-related activations (Nielson et al., 2002). It is possible that this recruitment represents age-related disinhibition of inappropriate circuits (Cabeza, 2002; Cabeza et al., 2000; Cabeza, Grady et al., 1997; Chao & Knight, 1997; Grady, 1998; Grady et al., 2006; Persson et al., 2007; Townsend et al., 2006). It is also possible that this recruitment represents a larger need for compensation due to the stress of aging, perhaps because more motor activation is needed to initiate coordinated movements based on specific stimulus-response associations. This is interesting, given that the greater the increase in sigma power during sleep recovery the greater the recruitment of right primary motor cortex activation during inhibitions the next day (see Table 3.3). Spindles have been associated with sleep-dependent motor learning (Walker et al., 2002; Walker, Stickgold, Alsop et al., 2005). It is possible old adults are relying on a more learned stimulus-response strategy following recovery sleep than a cognitive inhibition strategy to perform the task.

In conclusion, these data demonstrate that relationships between performance and brain activation differ by task variable, and that these relationships do not necessarily

generalize to old age. This is most apparent in that parietal and frontal activations are associated with performance in different ways in young and old adults. This also suggests that old adults respond fundamentally differently to sleep deprivation and subsequent recovery than young adults. This may reflect a difference in cognitive strategies employed or functional reorganization of brain networks due to aging. Whatever the reason, it is clear that any strategy (behavioral, physiological, or pharmacological) developed to manage the performance effects of sleep loss will need to account for age.

General Discussion

Processing inefficiency, functional reorganization, and changes in cognitive strategy: the case of sleep deprivation and attention shifting

Optimal daytime functioning requires adequate sleep quantity and quality. Over a hundred years of science leaves no question of this fact. This means that in order to perform most adaptively, one must be fully rested. This does not mean that one cannot perform if one is sleepy. Sleepy individuals perform all the time, and in fact, it is important to remember that the ability to perform while sleepy is a critical evolutionary advancement. If there is a food shortage, an organism may be served best by spending more time foraging for food. The same can be said about an organism that is threatened by its environment in the form of a predator or a natural disaster. One could argue, then, that we are biologically adapted to persevere in the face of sleep loss, to continue to act as we should in order to maintain survival. But, this ability to remain awake beyond what is optimal has its limits and its consequences. These consequences assault the brain and the body, resulting in diminished performance, altered task-related brain activation, and impaired immune and metabolic functioning (D. Dinges & Kribbs, 1991; Drummond & Brown, 2001; Durmer & Dinges, 2005; Kleitman, 1963; Spiegel et al., 1999; Spiegel et al., 2002; Williams et al., 1959). Prolonged sleep loss can even result in death (Bentivoglio & Grassi-Zucconi, 1997; De Manaceine, 1894; Rechtschaffen et al., 1983; Shaw et al., 2002). One can remain awake, depriving the body of what it needs, but not without cost; once again proving that age old adage, ‘there is no such thing as a free lunch’.

Over the last several decades, numerous labs throughout the world have explored the nature of these impairments of brain and body. It is clear that they occur, and that they cover a constellation of functions and physiological systems. Finding biological systems unaffected by sleep loss has now become the exception rather than the rule. Sleep loss itself, either in its acute total form or as chronic partial sleep restriction is now considered by many to be a generalized stressor eliciting a generalized stress response (Cirelli, Faraguna, & Tononi, 2006; Leproult, Copinschi, Buxton, & Van Cauter, 1997; McEwen, 2006; Shaw et al., 2002; Spiegel et al., 1999). Like other stressors, the body can adapt rather aptly when the stress is acute, and the effects can be entirely reversible upon adequate subsequent sleep to recover. If sleep loss becomes chronic, however, it can lead to allostatic build-up, which may have long term consequences (McEwen, 2006).

In terms of performance, even acute total sleep deprivation of one to two days results in decrements over a wide array of neurobehavioral domains. Associated with these performance changes are altered neuronal responses. Usually, these changes are most severe in frontal and parietal regions, though tasks employed by most studies target frontal-parietal circuits predominantly. Still, a level of consistency across studies and tasks remains. Frontal cortex, in particular, is dramatically affected by sleep deprivation showing the largest absolute and relative decreases in metabolic rate (Thomas et al., 2000). Increased recruitment of left frontal and parietal regions following sleep deprivation appears to be common and is often interpreted as a compensatory response (Chee & Choo, 2004; Drummond et al., 2000; Drummond et al., 2004; Drummond et al.,

2001). These data, amongst others, suggest that sleep deprivation affects the brain differentially. That is to say, some regions appear to be affected more than others, and some regions appear to be recruited to compensate in more circumstances than others. However, it is unclear why these changes are occurring.

Several possible explanations for these consistencies in the neural response to sleep deprivation exist. One possibility is that sleep deprivation results in decreased processing efficiency within certain brain regions, particularly within the frontal cortex. This processing inefficiency leads to reduced recruitment of frontal activation and impaired related performance. This explanation seems likely, especially given the data suggesting that among the greatest reductions in metabolic rate following sleep deprivation are those that occur within the frontal cortex (Thomas et al., 2000; Wu et al., 1991). Additionally, these regions show the largest reductions in activity during sleep (Braun et al., 1997; Kaufmann et al., 2006; Maquet et al., 1997; Nofzinger et al., 2002). The question then arises, why does frontal cortex respond so dramatically to sleep and sleep loss? It has been hypothesized that sleep protects against oxidative damage and reduces the build-up of oxidative stress, whereas continuous wakefulness increases the build-up of oxidative stress (McEwen, 2006; Schulze, 2004). Increasing glutaminergic neurotransmission, which makes up the lion's share of the brain's energy demands, increases oxygen metabolism (Attwell & Iadecola, 2002). Resulting from this is an increased risk for the build-up of oxidative stress (Schulze, 2004). The frontal cortex has been shown to be particularly vulnerable to oxidative stress (Crivello et al., 2005; Denisova et al., 2002). Thus, if sleep deprivation can lead to the build-up of oxidative

stress, it seems likely that frontal cortex will be more susceptible to this stressor, and may require more attention during sleep. This effect may not be limited to the frontal cortex. Other highly metabolically active, neuroplastic regions may also show this susceptibility. It may be that heteromodal cortex has a higher general metabolic demand than other regions leading to a greater build-up of oxidative stress; requiring a greater reduction during NREM sleep. This may explain why slow wave propagation occurs predominantly within frontal regions and migrates towards other association regions such as parietal cortex (Massimini et al., 2004). This is a particularly intriguing idea, since Tononi has posited the benefits of slow waves on synaptic downscaling and neurometabolic regulation (Tononi & Cirelli, 2003, 2006). Thus, slow wave sleep could perform three vital roles in a single action: 1) reduce metabolic demand in the cortex, 2) aid neuroplastic changes leading to improved learning and memory, and 3) reduce the effects of oxidative stress. Should sleep be deprived, oxidative stress would continue to build-up, as would metabolic demand. Eventually, metabolic resources would be too low, and the build-up of oxidative stress would be too great. Impairments would begin to occur. Performance impairments would begin to occur first in behavioral domains relying on those brain regions most susceptible to the build-up of oxidative stress and metabolic demand. This greater susceptibility could explain why frontal and parietal regions are so consistently affected by sleep deprivation.

Alternatively, parietal regions may be so prominently affected by sleep deprivation simply because attention is so greatly impaired by sleep loss and is so intimately interrelated with arousal processes. A recent report by Chee's group suggests

that lapses occurring after sleep deprivation are distinct from lapses occurring after normal sleep (Chee et al., 2008). That is to say, if you are sleep deprived, your lapses are more likely to be due to decreased thalamic and visual and parietal cortical activation which represents a sort of global disengagement from the environment. It lends evidence to the idea that lapses can reflect the occurrence of microsleeps. This idea can support the prefrontal susceptibility hypothesis as well. If lapses are microsleeps, and if microsleeps are transitions into NREM sleep states, then, as Massimini and Tononi suggest, decreased activation during laspses could reflect a breakdown of network connectivity (Massimini et al., 2005). Since the frontal lobes are involved with so many networks, it would appear as if the frontal cortex is more susceptible to sleep loss. These two possibilities are not mutually exclusive, and provide a sort of 'chicken or the egg' problem. Are the effects of sleep loss caused by the consequences of prolonged wakefulness or by the intrusion of influences from sleep-promoting centers on cortical functioning *due* to prolonged wakefulness? An interaction of these two mechanisms seems most likely to be the true cause of activation decreases following sleep deprivation.

Reduced processing efficiency and recruitability cannot explain the whole story, as some areas show increased activation, at least relatively, and these increases relate to improved or preserved performance (Drummond, Bischoff-Grethe et al., 2005; Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001; Drummond, Meloy et al., 2005). Another possible explanation is functional reorganization of task-related activation. That is to say, when stressed with sleep deprivation, the brain responds by changing the way activation leads to performance. This also seems likely as

studies have shown activations present only in the sleep deprivation condition can correlate with preserved performance ((Drummond et al., 2000; Drummond et al., 2001), see data from chapter 1). Drummond's data show this effect most clearly as sleep deprivation alters the relationship between task difficulty and brain activation (Drummond et al., 2004). In his study of logical reasoning, new, predominantly left, prefrontal regions showed increased activation as task difficulty increased in the sleep-deprived state. This effect has been interpreted to represent the utilization of cognitive reserves untapped in a less stressed condition, particularly if the new regions recruited represent homotypical activations, i.e. activations occurring in the same location as rest, but in the opposite hemisphere (Cabeza, 2002; Drummond et al., 2004). This interpretation necessitates that individuals are performing the same task in the same way in both rested and sleep-deprived conditions. The only difference between rested and sleep-deprived conditions would be the amount of neural work required to perform the same task. Since it is more efficient to utilize the minimum activation required to produce optimal performance, new activations should become apparent only when difficulty is sufficiently increased. This would make sense in light of reduced neural efficiency caused by sleep loss. More activation would be necessary to lead to the same performance output, whereas less activation would result in performance impairments. This is often observed in the imaging literature, where increased activations are associated with preserved performance and decreased activation are associated with impaired performance (Chee & Choo, 2004; Chee et al., 2006; Chee & Chuah, 2007; Choo et al., 2005; Drummond, Bischoff-Grethe et al., 2005; Drummond & Brown, 2001;

Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 1999; Drummond et al., 2001; Thomas et al., 2000; Wu et al., 1991). However, the data of Mu, Caldwell, and Chee show that those who generally have more activation at baseline are better off after sleep deprivation (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005). This would argue against the cognitive reserve hypothesis and the principle of neural efficiency, i.e. that needing to use less activation for the same performance would result in performing better when stressed by sleep loss. Additionally, it cannot simply be a matter of difficulty, since Drummond shows sleep deprivation alters the relationship between difficulty and brain activation.

A third possibility is that sleep deprivation may result in a shift in cognitive strategies employed to perform a task. Since different cognitive strategies are mediated by different neural networks, this, too, can explain the data. In fact, what seems most likely is that all three of these are true. More specifically, they are all probably part of the same explanation. The data from chapter 1 illustrates this point most effectively. When one is rested, the assumption is that one performs a task in a specific way, and that this way is consistent across subjects. This of course assumes a proper study environment, and the utilization of a well designed and validated task, such as the Posner task (Posner, 1980). The Posner task is designed to illustrate the effects of cues, be they central or peripheral, on reaction time performance within an individual. That is to say, if one is told where a target will appear, then that information will be used to direct attention towards the location where the target is suggested to appear. If this information is present and accurate, that individual will, in a general sense, respond more quickly than if it is

not. Utilization of cues, leading to the shifting of attention towards a predicted location in space that is behaviorally relevant, calls upon a network of frontal, parietal, and cingulate regions. When one examines, within an individual, those events where cues were utilized most effectively in comparison to those where cues were utilized least effectively, posterior cingulate activation becomes apparent (Mesulam et al., 2001; Small et al., 2003). This represents a very specific brain-performance relationship, which was interpreted to suggest the generation of a motivational bias for a particular location in space based on predictive information, i.e. the cue. In plain terms, this means that when one sees a cue, one interprets it to suggest where it would be most adaptive to shift attention. But, as seen in chapter 1, activation of this region was not noted in the sleep deprivation condition, and the benefit of the cue was less apparent behaviorally. Instead, we observed an increase in activity in the left medial parietal cortex during the fastest trials. Posterior cingulate cortex (PCC) activation was not observed in any circumstance following sleep deprivation. One can hypothesize from this that sleep deprivation led to a change in the utilization of PCC activation due to decreased recruitability or processing efficiency within this region. This then results in an inevitable compensatory reorganization of activation associated with the task, probably *because* of a change in cognitive strategy. In this case, we posit that the change in strategy is one that relies on susceptibility to exogenous attention capture by target appearance. The task is still being performed, and attention shifts are still occurring. In this case, the way the brain functionally organizes these attention shifts is altered by a change in cognitive strategy, which necessitates that functional reorganization. You are still shifting attention, but the

way you shift attention now differs. It is unlikely to be due to inefficiency alone, because sleep deprivation resulted in increased activation of medial parietal regions when responses were faster. It is unlikely to be due solely to functional reorganization while using the same strategy, because the behavioral profile changed in such a way that cues no longer provided a general behavioral advantage to response time. This was, importantly, apparent despite no clear overall reaction time differences. Functional reorganization implies that the same performance would be produced by different activation patterns. Thus, aspects of processing efficiency, functional reorganization, and change in cognitive strategy can all be part of the same process of adapting to the effects of sleep loss.

Though this is merely an interpretation, this highlights one important fact. For some reason, sleep-deprived individuals do not perform the same task in the same way, and do not use the same brain regions in the same way to perform that task. Specifically, in the case of the data from chapter 1, something about sleep deprivation results in the inability or the change in preference to utilize the posterior cingulate cortex to aid attention shifting. The reason for this remains unclear; however, my hypothesis from the introduction suggests that a root cause of this may be gleaned from what occurs in the transition to NREM sleep. Namely, regions whose activity is suppressed by transition into NREM sleep may be the most susceptible to impaired recruitment and processing inefficiency following sleep deprivation. PCC activity is suppressed in NREM sleep, and medial parietal cortex activity is not (Braun et al., 1997; Kaufmann et al., 2006; Maquet et al., 1997; Nobre et al., 2000; Nofzinger et al., 2002). Thus, if the occurrence of lapses

may represent, in at least some cases, a transition into NREM sleep, then regions suppressed by NREM sleep may be intermittently suppressed in a sleep-deprived state. This intermittent suppression could impair processing efficiency due to intermittent hyperpolarization of PCC neurons, which may also affect interregional effective connectivity, as Tononi's data suggest (Massimini et al., 2005). The fallout of this is that processing the cue may become too difficult on a neural level, and thus subjects shift to a differing cognitive strategy to perform the task; one that is reactive, rather than proactive. This new strategy is perhaps adequate, but it is certainly not optimal.

An alternative explanation is that the suppression of PCC activation results in the disinhibition of parietal activation. Indeed PCC and parietal regions reciprocally inhibit each other (Constantinidis & Steinmetz, 2001). This concept of disinhibition of inappropriate circuits has been suggested in the aging literature, for example, where lateralization of activation becomes less apparent. However, in the case of the data in chapter 1, this is not likely. If disinhibition of parietal activity was apparent, then one would not see it preferentially for faster performance. Thus, parietal activation in the sleep-deprived state must represent some change in brain-behavior relationships. We interpret this to be manifest of a change in cognitive strategy employed to perform the task, which leads necessarily to the functional reorganization of task-related activation. This, in turn, highlights a principle of sleep deprivation, which is that some neural networks are more susceptible to its effects than others. I posit that the networks most susceptible will be ones actively suppressed on the transition into NREM sleep which, if repeatedly and intermittently suppressed following sleep deprivation, can lead to residual

impairments of connectivity and recruitability even when these regions are not suppressed and the individual is awake and responding.

Age, sleep loss, and brain function: do the effects of sleep loss generalize to old age?

Surprising parallels exist between the sleep deprivation and aging literature, and yet no functional imaging studies have compared the effects of the two directly nor studied their interaction. Both age and sleep deprivation have been shown to influence task-related brain activation and related performance with a particular emphasis on frontal susceptibility (Harrison et al., 2000; Rypma & D'Esposito, 2000; Thomas et al., 2000; R. L. West, 1996). These effects were also observed in the present report, in the case of the data from chapter 2. More specifically, when performing a go/no-go task, aging reduced task-related activation within superior frontal cortex, dorsal anterior cingulate, and bilateral insula. Sleep deprivation reduced activation within right superior and ventral frontal cortex and left insula. Hence, some sleep loss related reductions in activation in young adults were also observed in old adults at baseline. Performance associated with these activations, i.e. selecting the correct response, was impaired by sleep deprivation and by age at baseline. In addition, activation within right ventral lateral prefrontal cortex was similar at baseline and similarly reduced after sleep deprivation. Performance associated with this activation was similar across age group, and similarly impaired by sleep deprivation. Four regions demonstrated a significant age by sleep condition interaction: left dorsal lateral prefrontal cortex, right superior frontal sulcus, anterior cingulate cortex, and left insula. All of these regions have been

associated with cognitive control and contextual responding (Bush, Luu, & Posner, 2000; Critchley, 2005; Garavan et al., 2002; Garavan et al., 1999; Heekeren et al., 2004; Heekeren et al., 2006; Rowe et al., 2000; Rubia et al., 2001). This suggests age and sleep loss can impair performance on cognitive tasks at the level of cognitive control and not just at the level of sensory processing or motor output of responses. These activations further suggest a frontal lobe susceptibility to age, sleep deprivation, and also their interaction, though this susceptibility is not exclusive to frontal cortex.

The aging literature demonstrates that at baseline young and old adults perform the same task using different neural mechanisms (Backman et al., 1997; Cabeza, 2002; Cabeza, Grady et al., 1997; Cabeza, McIntosh et al., 1997; Della-Maggiore et al., 2000; Duverne, Motamedinia, & Rugg, 2008; Grady, 1998; Grady et al., 1998; Grady et al., 1995; Nielson et al., 2002; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000). This generally results in reduced lateralization of task-related activation across a variety of tasks (Cabeza, 2002; Cabeza, Grady et al., 1997; Della-Maggiore et al., 2000; Grady, 1998; Grady et al., 1998; Nielson et al., 2002; Reuter-Lorenz et al., 2000), though this effect predominates in adults whose age-related decline is larger (Duverne et al., 2008; Nielson et al., 2002). For working memory abilities such as response selection, older adults show impaired dorsal lateral prefrontal activation, with relatively preserved ventral lateral prefrontal activation (Rypma & D'Esposito, 2000). We replicate this observation in chapter 2. For the response selection contrast, superior frontal sulcus activation was noted in young adults, but not in old adults. Instead, ventral medial prefrontal cortex activation was noted in old adults. These data suggest that at baseline, old adults are

utilizing different neural mechanisms to perform the same cognitive actions. Because of this, the neural effects of sleep deprivation will necessarily be different in both age groups. Young adults experience reduced activation in right superior frontal cortex, whereas old adults do not. Young adults experience a reduction in response selection performance, i.e. they will make more errors of omission, whereas old adults do not. The response selection performance of old adults is already impaired at baseline, a state where old adults show reduced related bilateral superior frontal sulcus activation.

Since our data and the data from others (Rypma & D'Esposito, 2000) suggest that dorsal prefrontal recruitment is impaired with aging, one would expect that any sleep deprivation related compensatory activations within the dorsal prefrontal cortex would be present only in the young. As with the data in chapter 2, we show this to be the case. Following sleep deprivation, when young adults are inhibiting inappropriate responses, they recruit more left dorsal lateral prefrontal cortex, while old do not. Interestingly, this recruitment aided in the minimization of lapses rather than inhibitory errors. If successfully performing a cognitive task requires the interaction of multiple neural networks (Dosenbach et al., 2007), it is possible to view that impairments within any of these interacting networks may result in compensatory over-recruitment in others. For instance, in the case of the data from chapter 2, sleep deprivation results in impaired right prefrontal recruitment which results in impaired inhibitory performance (see chapter 4, Table 4.2, Figure 4.5). Specifically, when the ability to stop a prepotent response is impaired, mechanisms involved with priming which responses are go and which are no-go (superior frontal cortex) may be recruited to compensate. This may have the effect of

keeping individuals on task and responding to go trials, but it may not be able to aid in the ability to inhibit prepotent responses. This suggests that following sleep deprivation, there may be a shift in emphasis of which processes are relied on to produce appropriate behavioral output.

Old adults increase activation in the anterior cingulate while they make errors. This activation could be compensatory, i.e. old adults increasing error detection related activations within the anterior cingulate to prime error remedial actions (Dehaene et al., 1994; Eichele et al., 2008; Garavan et al., 2002; Matthews et al., 2005). However, this activation appears to be located more ventrally than traditional error detection related activations within the anterior cingulate (Eichele et al., 2008; Garavan et al., 2002; Matthews et al., 2005). Previous studies have demonstrated a clear functional distinction between dorsal and ventral anterior cingulate, with dorsal regions being more associated with cognitive control of motor actions and ventral with more affective processing (Bush et al., 2000). That said, studies have shown activations within these regions in response to errors and omissions in expected rewards (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Specifically, the rostral cingulate zone becomes more active when there is an apparent need to adjust behavior in order to achieve a desired goal. From a network perspective, a recent report implicated two distinct networks which adapt control on a trial by trial basis and maintain task mode (Dosenbach et al., 2007). In this data set, graph analysis was used to identify linked 'hubs' of ROIs and regions disconnected from all other regions in the analysis. One network consisted of lateral frontal and inferior parietal regions that adapted responses on a trial by trial basis, with the other network

consisting of anterior cingulate and anterior insula maintaining task mode throughout the run. Since sleep deprivation impairs right lateral frontal recruitment and since left dorsal lateral frontal recruitment is impaired with age, old adults may rely on recruiting activity within the second network. That is to say, while performing a go/no-go task, frontal and parietal regions may allow the flexible response pattern of selecting appropriate go responses and inhibiting inappropriate no-go responses on a trial by trial basis. At the same time, a network of cingulate and insula regions may allow for the online maintenance of task instructions, and monitor for behavioral deviations from this task mode. Where young adults may rely on the trial by trial network to compensate, old adults may rely on the maintenance of task mode to compensate.

Alternatively, this increased activity in rostral anterior cingulate may reflect greater disinhibition of the default mode network (Gusnard et al., 2001; Raichle et al., 2001). Studies of aging have shown that old adults show more default mode activity than young adults across a variety of tasks, and that this disinhibited default mode activity relates to greater age-related declines in performance (Grady et al., 2006; Persson et al., 2007). A recent study suggests that a general mode of gradual disinhibition of default mode, task irrelevant regions can lead to the generation of errors up to 30 seconds later (Eichele et al., 2008). So, if older adults show a general greater disinhibition of default mode activation, the inclusion of the stress of sleep loss may increase this further leading to more errors.

Age not only alters the effects of sleep deprivation on performance and brain function, but also alters the relationship between these variables. This becomes apparent

when examining the data from chapter 4 in tables 4.2 and 4.4. In these analyses, performance change for go and no-go events is regressed against whole brain activation change from SO to Sd conditions. For young adults, reduced inhibitory performance is associated with reduced activation in both right prefrontal cortex and the right occipitotemporal area. Both of these areas are recruited in baseline conditions, as is observed in Figure 4.5. This analysis suggests that changes in activation within these regions in particular relate to changes in inhibitory performance. Activations within these regions associated with go/no-go tasks have been reported in a number of studies (Booth et al., 2003; Garavan et al., 2002; Garavan et al., 1999; Rubia et al., 2001). Old adults show no significant relationship between activation change and no-go performance. This suggests that right prefrontal and occipitotemporal activation may relate less to successful inhibitory performance in old adults. How no-go performance change after sleep deprivation relates to brain activity in old adults remains unclear, and future, better powered studies will have to examine this more closely.

With regard to lapses, loss of left inferior parietal cortex related to the occurrence of more lapses (see chapter 4, Table 4.4, Figure 4.4A). Left parietal activation change at a similar location has been reported in multiple functional imaging studies of sleep deprivation (Chee & Choo, 2004; Chee et al., 2006; Drummond, Bischoff-Grethe et al., 2005; Drummond et al., 2000; Drummond et al., 2004; Drummond et al., 2001; Lim et al., 2007; Thomas et al., 2000). In some, this activation has been associated with preservation of performance after sleep deprivation (Drummond et al., 2000), increased task difficulty (Drummond et al., 2004), or fast response times on the PVT (Drummond,

Bischoff-Grethe et al., 2005). Recently, Chee's group has shown that reduced left inferior parietal activation occurs during lapses after sleep deprivation (Chee et al., 2008), though the locus in his study is more medial than what is presented in the current report. These data, along with the data presented in chapter 4, pose a difficult problem. We know that following sleep deprivation reduced left inferior parietal activation is associated with increased lapses, whereas increased parietal activation is associated with reduced lapses. What we do not know is the causal direction of this relationship. Do lapses occur because parietal activation is decreased, or does parietal activation decrease because of lack of information flow from thalamic and visual regions due to the onset of lapses (Chee et al., 2008)? In other words, is preserved parietal activation compensatory, or is it simply an effect of getting fewer lapses? It seems that both of these possibilities can be true. If activation increases above what is observed in the rested condition and if this increase relates to preserved performance, then it would seem parietal cortex is compensating for the effects of sleep loss (Drummond et al., 2000; Drummond et al., 2001; Wu et al., 1991). On the other hand, the thalamus has been proposed to play a mediating role in the interaction between attention and arousal (Portas et al., 1998). This point is further argued by Chee's data (Chee et al., 2008), in that thalamic and visual cortex activity reductions occur during lapses. From a neuroanatomical perspective, it makes sense that sleep promoting neurons in the preoptic area of the hypothalamus will act to alter thalamic activity and inhibit cortical activity, and this has been demonstrated in animal studies (Gvilia et al., 2006; Saper et al., 2001). However, this is not a one way street, and Saper has shown that cortical inputs can feedback onto the ventral lateral

preoptic nucleus of the hypothalamus to influence its activity. Thus, lapses may occur due to a shift in the brainstem, thalamic, and hypothalamic interactions between wake-promoting and sleep-promoting neurons towards transient "sleep on" neuron domination. This, in turn, can affect cortical activity, leading to decreased activation. But, cortical activity can feedback onto this sleep/wake flip flop switch promoting wakefulness and reducing the risk for lapses. In the case of our data from chapter 4, young adults who increased activation above baseline showed a minimal increase in lapses (1.7%±2.1%), whereas those that did not showed a drastic increase in lapses (19.1%±5.4%). These data argue that left parietal activation is indeed compensatory, and minimizes the occurrence of lapses.

The opposite relationship was detected in old adults within the same left inferior parietal regions and within dorsal anterior cingulate cortex. That is to say, old adults that increased activation above baseline in the Sd condition had more lapses (see chapter 4, Table 4.4, Figure 4.4B). Nielson's go/no-go data in old adults shows increased left parietal activation (Nielson et al., 2002). This activation increase is largest in old adults with the poorest performance. These data demonstrate that for old adults, left parietal activation increases are not compensatory, and in fact increase the occurrence of lapses. This demonstrates that the effects of sleep deprivation on brain function do not generalize across age groups. Further, the way in which sleep deprivation affects the way in which brain activation relates to performance also does not generalize to across age groups.

As stated above, increased activation within dorsal anterior cingulate cortex during go events was associated with old adults having more lapses. These data suggest

that the increased activation within the anterior cingulate during errors may also result in more lapses. However, this activation did not correlate with lapse performance. Thus, old adults that increase activation in the anterior cingulate specifically during go responses showed more lapses. Dorsal anterior cingulate activity has been associated with error detection (Dehaene et al., 1994; Garavan et al., 2002; Matthews et al., 2005), which is followed by a reduction in task-irrelevant activation and a re-engagement of task-relevant activations (Eichele et al., 2008). Activation in this region during correct performance may relate to erroneously marking the response as an error of commission, which could result in a shift towards a more cautious response strategy. This hyper recruitment of dorsal anterior cingulate may relate to compensation in the face of sleep deprivation. Aging results in decreased error-related responses within the anterior cingulate, and this yields diminished error remedial actions (Falkenstein et al., 2001). This effect has been interpreted to reflect alterations in error detection processes with age. With the added stress of sleep deprivation, it is possible that increased activity within dorsal anterior cingulate reflects an attempt to compensate for a general sense of impaired performance. Old adults may know they are performing more poorly, but they may be impaired at detecting impairments on a trial to trial basis. Thus, anterior cingulate activation is increased during errors *and* during correct responses, supporting a more critical view of performance in general. This effect is similar to that observed in patients with obsessive-compulsive disorder, whereby cingulate activation is increased for correct and erroneous responses (Ursu, Stenger, Shear, Jones, & Carter, 2003). In old, sleep-

deprived participants where increased anterior cingulate activation occurs during correct go trials, an incorrect detection may lead to an increased tendency to lapse.

Taken together, these data represent a fundamental principle of aging, which is that since aging alters the way in which brain function relates to performance, stressing an aged brain with sleep deprivation will result in a different response than stressing a young brain with sleep deprivation. Further, mechanisms employed to compensate for sleep deprivation will likely be different since different mechanisms are employed to perform the task at baseline. It seems likely to me that the reason for this change is that aging already impairs processing efficiency in certain brain networks, particularly ones relying on dorsolateral prefrontal functioning. This is demonstrated by our data from chapter 3 showing an altered relationship between right prefrontal activation at baseline and inhibitory performance. The reason this relationship is altered is that old adults show, in general, impaired right prefrontal recruitment. Those old adults that can recruit right prefrontal cortex show baseline inhibitory performance that is as good as the best young performers. This age-related shift in baseline brain-behavior relationships will in turn cause a shift in the way in which tasks are being performed at the neural and probably cognitive level. That shift will most likely rely on a different set of resources that can be pulled online to compensate for further stressors. This is evidenced by our data in chapter 2 and chapter 4. Young adults, when sleep deprived, increase left prefrontal activation. This is associated with the minimization of performance errors, mainly lapses. At the same time, maintenance of right lateral prefrontal cortex results in minimized errors of commission. Old adults do not show a compensatory over-

recruitment of left dorsal lateral prefrontal cortex, and right lateral prefrontal activation does not relate to performance change. Recruitment of dorsal prefrontal cortex is already reduced at baseline in old adults, as has been observed by others (Rypma & D'Esposito, 2000). Instead, increased activation was observed in old adults within the rostral anterior cingulate during errors, an area associated with error monitoring and default mode activation. If one applies the model of Dosenbach and colleagues (Dosenbach et al., 2007), young adults appear to compensate for sleep deprivation by further relying on a cognitive control network that adapts behavior on a trial by trial basis, whereas old adults rely on a network that maintains task set across the testing period.

Aging alters how individuals recover from sleep loss

Though a multitude of studies have examined the effects of sleep loss on brain function and performance, much less is known about the recovery from sleep deprivation following subsequent sleep. Studies have generally shown that after recovery sleep, both behavior and physiology return to normal (Belenky et al., 2003; Bonnet, 1985, 1989; Bonnet & Arand, 1989; Gosselin et al., 2005; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Patrick & Gilbert, 1896; Rosa et al., 1983; Spiegel et al., 1999; Spiegel et al., 2002; Williams et al., 1966; Williams et al., 1959). This behavioral and physiologic recovery occurs after a relatively short period of sleep, which is most dramatically demonstrated by the study of Kales and Dement where the effects of 200+ hours of continuous wakefulness is apparently recovered after a few nights of sleep (Gulevich et al., 1966; Johnson et al., 1965; Kales et al., 1970). In contrast, subtle

performance differences can still remain after recovery sleep (Belenky et al., 2003; Herscovitch & Broughton, 1981; Rosa et al., 1983; Williams et al., 1966; Williams et al., 1959). A recent study by Wu shows that metabolic activity within the prefrontal cortex has not yet returned to baseline after one night to recover (Wu et al., 2006). While data suggest that sleep deprivation affects brain function differentially throughout the brain, it is then not surprising that the recovery of brain function upon subsequent sleep occurs at a differential rate throughout the brain. These data suggest that prefrontal function and related behaviors may show delayed recovery.

The data from chapter 3 support this notion. In terms of inhibitory performance, though nonsignificant, both young and old adults show a trend for decreased inhibitory performance after one night to recover from sleep loss (see chapter 3, figure 3.5). Associated with this are differences in prefrontal activation that have persisted from the Sd condition to the SR condition. Specifically, there were persistent reductions of right prefrontal cortex activation associated with inhibition events, and young adults show a persistent increase in left dorsal lateral prefrontal cortex (see chapter 3, Figure 3.6). For young adults, right prefrontal activation is associated with preserved performance (see chapter 3, MRI data section, and chapter 4, Table 4.2).

Old adults show a different neural response following recovery sleep. Increased right insula and bilateral fusiform activation resulted in fewer lapses, whereas greater right primary motor and premotor activation resulted in more inhibitory errors and lapses, respectively. Dosenbach and colleagues show that insula and fusiform regions are part of a network of functionally connected regions that maintain task mode across a testing

period (Dosenbach et al., 2007). As hypothesized above, this network may be utilized by old adults to compensate in light of reduced recruitability of dorsal frontal regions associated with cognitive control on a trial by trial basis. After the sleep recovery condition, old adults do appear to perform better when these regions are recruited. In contrast, old adults that show more right hemisphere motor related activation change are more likely to do more poorly after sleep recovery. Since the task was performed in only right handed people, left motor activity is expected during go responses. However, as Cabeza proposed, functional asymmetry is reduced in old age (Cabeza, 2002), and as Nielson and Duverne have shown, this reduction in functional asymmetry can prove maladaptive (Duverne et al., 2008; Nielson et al., 2002). It is possible that these old adults are relying on a more learned stimulus-response strategy following recovery sleep than a cognitive inhibition strategy to perform the task, whereas those that recruit insula and fusiform regions may be relying on a strategy more related to the maintenance of task set. These compensations may be occurring in light of a persistent reduction of right lateral prefrontal activation. Data from chapter 3 and 4 highlight how performance and neural recovery from sleep deprivation may not be complete after one night. These data also highlight that age alters the specifics of this effect. That is to say, age impacts how the brain responds to sleep loss, and how recovery sleep impacts this response. Of note is that young and old adults utilize what may be compensatory activations following sleep deprivation. These activations appear to have limited effect on performance after total sleep deprivation. However, if similar activations are utilized in the recovery condition, they predict preserved performance. Specifically, young adults utilize left frontal-parietal

activations to preserve go and no-go performance in the Sd condition. These regions have been shown to be part of a network of cognitive control regions that adapt performance on a trial by trial basis (Dosenbach et al., 2007). In contrast, old adults recruit a network of anterior cingulate, insula, and fusiform regions to preserve go and no-go performance. These regions are part of a relatively distinct network of regions associated with maintaining task mode throughout a testing period (Dosenbach et al., 2007). In light of these data, I hypothesize that old and young adults compensate for sleep loss by relying on distinct mechanisms to regulate cognitive performance. These mechanisms may have limited effect in a total sleep deprivation paradigm, but may have functional importance in cases where the effects of sleep loss are more mild, e.g. after a few hours of extended wakefulness or after a night of recovery sleep.

Though a night to recover from sleep deprivation may result in diminished performance impairments and brain activation changes, the way in which nighttime recovery sleep relates to these changes remains relatively unexplored. We examine this in detail in chapter 3. Though young and old adults were given the same sleep opportunity in baseline and recovery conditions, young adults slept roughly an hour longer, showed greater sleep efficiency, and lower amounts of wake after sleep onset regardless of condition. In terms of staging, young adults showed a greater amount of slow wave sleep and a greater percentage increase in slow wave sleep from baseline to recovery conditions. At the same time, young adults showed a small decrease in percent stage 2 sleep, whereas old adults showed a small increase in percent stage 2 sleep. This probably reflects the age-related reduction of slow wave amplitude below the cut-off

criteria of Rechtschaffen and Kales (Rechtschaffen & Kales, 1968), resulting in a categorization of slow wave sleep as stage two. Despite this, old adults still showed a significant increase in slow wave sleep percentage from baseline to recovery conditions. These data are canonical of the aging and sleep literature (Feinberg & Carlson, 1968; Kales et al., 1967; Van Cauter et al., 2000; Webb & Campbell, 1979, 1980). Analysis of spectral data corresponded with these numbers. Delta power, the frequency range of slow waves, was higher in young adults in both conditions and increased more in young adults in the sleep recovery condition (see chapter 3, Figure 3.1). The slope of exponential decay of delta power across the night was increased in both age groups from baseline to recovery sleep (see chapter 3, Figure 3.2). Unlike Dijk's data (Dijk et al., 1989), we did not see a reduced slope of delta dissipation across the night in old adults. We also did not see a significant difference between age groups in the amount of slope increase from baseline to recovery conditions, though such a difference looks plausible when examining Figure 3.2. These lack of differences may be an issue of power; one future studies can address. Examination of sigma power, the frequency range for spindles, showed that, similar to delta power, young adults had higher sigma power than old adults in both conditions. Additionally, while young adults showed lower sigma power at the beginning of the night which increased throughout the night, old adults showed fairly stable sigma levels across the night. This was reflected in the difference in sigma slope across age groups. Interestingly, in both age groups, slopes were more positive after sleep deprivation. It is important to note, however, the near zero slope in old adults versus the obviously positive slope in young adults. The change in delta and

sigma power across the night demonstrates a generally reciprocal relationship between slow waves and sleep spindles, two prominent rhythms of NREM sleep (Dijk et al., 1993). In the current report, we find that recovery sleep is associated with an increase in delta power preferentially within the first part of the night, and an increase in sigma power preferentially within the second part of the night. This suggests that homeostatic dissipation of the sleep drive may involve more neurophysiologic systems than those associated with delta power alone. This would explain why individuals who sleep 4-6 hours per night still report increased sleepiness and impaired performance even though delta power has reached nearly end of the night levels within the first 4 hours (Belenky et al., 2003; Blagrove et al., 1995; Borbely et al., 1981; D. F. Dinges et al., 1997; Van Dongen et al., 2003; Webb & Agnew, 1974).

Since the loss of sleep alters task-related brain activation, one would expect that sleep following sleep deprivation would relate to the recovery of task-related brain activation the next day. In chapter 3, we show this to be the case. Specifically, right lateral prefrontal cortex activation associated with inhibitory control is reduced by sleep deprivation, and this reduction relates to impaired inhibitory performance (see chapter 2, Table 2.1, chapter 4, table 4.2). This reduction is more mild in young adults after recovery sleep (see chapter 3, Figure 3.6). The greater the increase in early night delta power from baseline to recovery sleep, the bigger the difference in baseline and recovery activation within the right prefrontal cortex (see chapter 3, Figure 3.7). This relationship is unintuitive. Further examination related this change in delta and sigma to next day performance. Those that increased delta relatively more than they increased sigma had

better performance recovery and lower levels of right prefrontal recruitment. This suggests that young adults who are not recovered may recruit more right prefrontal activity to compensate. Young adults show a similar relationship within the putamen (see chapter 3, Table 3.2), a region associated with acting on stimulus-response associations (Grahn, Parkinson, & Owen, 2008).

Old adults did not show the same relationship between delta power and next day brain activation (see chapter 3, Figure 3.7). This is interesting in light of the fact that old adults show substantially lower levels of delta power and persistently reduced right prefrontal activation following recovery sleep (see chapter 3, Figures 3.1 and 3.6, respectively). Instead, old adults that have a smaller increase in early night delta have a larger increase in activity within parietal and occipital regions during next day inhibition events. Right hippocampus was more active during inhibition events in old adults that had larger relative increases in delta power. All of these activations may represent compensatory activations in light of a continued reduction of right prefrontal activation. The greater the increase in late night sigma power in old adults, the smaller the difference in right primary motor activation between baseline and recovery conditions. This is particularly relevant given that the more old adults increased activation in right primary motor cortex in the recovery condition, the more inhibitory performance was impaired. These data not only show that age alters how recovery related-delta power increases at night relate to daytime brain function, but also show that nighttime delta may not restore task-related brain activation to baseline in old adults. Instead, old adults may rely more on sigma power to restore task-related brain activation to baseline. It is unclear why old

adults rely more on sigma power to recover. One possible explanation is that older adults rely more on a learned stimulus-response strategy to perform the task in light of reduced task-related dorsal prefrontal recruitment. Spindles have been shown to result in improved motor learning, and this improvement has been associated with changes in right primary motor activation (Walker et al., 2002; Walker, Stickgold, Alsop et al., 2005). Thus, old adults, in the face of reduced task-related dorsal prefrontal activation and reduced night time slow wave sleep and delta power compensate by relying on learned sensory-motor associations to perform the task, which is really a motor inhibition task.

Taken together, these data suggest that age alters sleep, alters the way in which sleep physiology relates to daytime brain activation, and alters the way in which this brain activation relates to performance. These data argue that old adults respond to sleep loss differently, because they perform tasks differently on a neurophysiological level. This difference probably stems from differences in task-related activation at baseline. These data argue that old adults respond to recovery sleep differently, probably because age alters the physiology of sleep. But further, these data suggest that nighttime changes in sleep variables from baseline to recovery sleep affect recovery of daytime brain activation differentially in young and old adults. That is to say, young adults recover normal right prefrontal activation due to changes in early night delta, whereas old instead show changes related to late night sigma and do not show recovery of right prefrontal activation. These data do not represent the whole story, and perhaps both age groups rely on both sleep variables to recover daytime task-related brain activity to baseline. This is evidenced in that both early night delta and late night sigma increase from baseline to

recovery sleep in both groups. Though these data form a complicated story, they highlight a general principle, which is that since age alters the way in which one performs a task and that because of this, the stress of sleep loss will have differential effects on brain function. Compensating for these differential affects will rely on distinct neural mechanisms, as will recovering from these effects. Any attempts to manage the performance effects of sleep loss or improve the performance effects of sleep recovery will need to carefully consider the impact of age on these sleep-brain-performance relationships.

Aging alters how baseline brain activity predicts behavioral responses to sleep loss and recovery

Since age-related differences in response to sleep deprivation may be due to age-related differences that exist at baseline, it becomes important to examine if age alters the relationship between baseline brain activation and subsequent change in performance following sleep deprivation and recovery. The response to sleep deprivation varies fairly widely across individuals (Leproult et al., 2003; Van Dongen et al., 2004; Van Dongen et al., 2007; Webb & Levy, 1984; R. T. Wilkinson, 1961), and this response is particularly stable within an individual (Van Dongen et al., 2004; Van Dongen et al., 2006; Webb & Levy, 1984). It has been shown that at least one component of this variance is independent of previous sleep history (Van Dongen et al., 2004). Since performance change following sleep deprivation differs so much between people, many researchers began wondering if this effect could be predicted at baseline. In a few relatively recent

studies, baseline brain activation was associated with performance change following sleep deprivation. In these studies, showing higher baseline activation throughout the cortex was associated with preserved performance (Caldwell et al., 2005; Mu et al., 2005). In a study by Chee's group, higher baseline activation within left parietal and frontal regions was associated with preserved performance (Chee et al., 2006). These data begin to give us an understanding of how the individual response to sleep deprivation may relate to the general availability of functional resources within fronto-parietal cortex. However, all these data come from young adults performing working memory tasks. What is not clear is whether these baseline activations can predict performance impairment due to sleep loss in old adults and in young adults performing different cognitive tasks. That is to say, how generalizable are these baseline predictions?

Data from chapter 4 address this issue, examining the relationship between baseline brain activation and go and no-go performance change following sleep loss and recovery in young and old adults (see chapter 4, Tables 4.1 and 4.3, Figures 4.1 and 4.2). The most obvious result is that young and old adults do, indeed, show different relationships between baseline brain activation and performance change following sleep deprivation. Young adults who recruit more rostral anterior cingulate activation at baseline during inhibition events show larger drops in performance after sleep deprivation which persists to a greater degree after sleep recovery (see chapter 4, Table 4.1., Figure 4.1A-B). Recruitment of anterior cingulate activation during inhibitions has been associated with a more absent-minded attitude that is prone to more cognitive

failures (Garavan et al., 2002). However, the locus of the activation reported by Garavan's group is more dorsal from our locus of activation. Alternatively, this activation may relate to a general disinhibition of default mode activation during no-go events (Gusnard et al., 2001; Raichle et al., 2001). Subjects who suppress default mode less at baseline may be more prone to errors in a sleep-deprived condition. That is to say, participants more able to focus on the task at hand and the cognitive actions required to perform that task successfully may be more resilient when stressed with sleep loss. Indeed, the degree to which task-related fronto-parietal activation correlates negatively with default mode activation relates to the degree of attention performance variability (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Sleep deprivation, particularly during slowed responses, is associated with impaired attention and disinhibited default mode activity (D. Dinges & Kribbs, 1991; Drummond, Bischoff-Grethe et al., 2005). Thus, one more able to inhibit default activity at baseline may be more able to inhibit default mode activity after sleep deprivation as well.

Young adults that recruit more thalamus activity during go events and parietal activation during no-go events were more likely to perform better after sleep deprivation and recovery, respectively (see chapter 4, Tables 4.1 and 4.3, Figure 4.2A-C). This relationship between baseline parietal activation and preserved performance is consistent with previous studies (Chee et al., 2006; Mu et al., 2005). Chee's recent data suggest that when lapses occur during the sleep deprived state, they are more likely to involve the suppression of thalamic and parietal activity (Chee et al., 2008). In light of these data, greater thalamic and parietal activation at baseline may reflect a greater ability to resist

suppression of activity after sleep deprivation. Interestingly, for our inhibitory task, no baseline activations within the prefrontal cortex predicted the response to sleep deprivation or recovery. This may be an issue of power in the present study, or it may be that go/no-go task-related prefrontal activation does not vary that widely between young adults at baseline. The data from chapter 4 suggest that the results of Chee and Mu do generalize to a certain extent beyond young adults performing working memory tasks (Chee et al., 2006; Mu et al., 2005). These data go along with a general theory of fronto-parietal susceptibility to sleep deprivation, and the importance of greater activation of these regions to resist the effects of sleep deprivation and more ably recovery from them.

The data from the current report suggest that the results in young adults do not generalize to old adults. It appears, instead, that baseline activation in different regions relate to performance change after sleep deprivation in old adults. Specifically, greater baseline left prefrontal cortex activation during no-go events and greater baseline midline cingulate, right supplementary motor area, right fusiform, and left parietal activation during go events relate to worse performance after sleep deprivation (see chapter 4, Tables 4.1 and 4.3, Figure 4.1C-D). With regards to left prefrontal activation, old adults show greater left prefrontal activation at baseline than young adults (see chapter 3, MRI data). Left prefrontal activation is increased in young adults following sleep deprivation and recovery (see chapter 2, Table 2.1, Figure 2.2B, chapter 3, Figure 3.6). This activation has been shown to be compensatory in young adults. It may be that old adults who recruit more left prefrontal activity at baseline are already compensating for the effects of age and are more susceptible to the effects of an additional stressor such as

sleep loss. For go events, greater right motor (midline cingulate, supplementary motor area) and visual (fusiform) related activations at baseline predict worse performance after sleep deprivation. Old adults who rely more on activations associated with the generation of stimulus-response associations and less on activations associated with cognitive control at baseline may be more likely to increase recruitment of these regions after sleep deprivation and recovery. As discussed in the sections above, increased recruitment of such regions within dorsal anterior cingulate, right primary motor, and right premotor cortex resulted in greater impairment in old adults. Thus, baseline activation of such regions may reflect a non-optimal behavioral strategy which is more susceptible to the effects of sleep loss.

Old adults that recruit more parietal, right prefrontal, and posterior cingulate activations at baseline during go events show preserved performance (see chapter 4, Table 4.3, Figure 4.2D-F). Greater baseline parietal activation relating to preserved performance is similar to the results in young adults, except these activations are associated with go rather than no-go performance. Thus, old and young adults may utilize similar regions at baseline, but they may utilize them for distinct aspects of performance. Interestingly, increased recruitment of right superior frontal activation during go events relates to preserved performance in old adults. This region is in a similar location to that observed in young adults at baseline during response selection events. Old adults, as a group, do not recruit this region, but instead recruit ventral medial prefrontal activation (see chapter 2, Table 2.4: B1). It may be that old adults that are still able to recruit this region during go events at baseline are more resilient after

sleep deprivation. Dorsal prefrontal recruitment associated with response selection abilities is impaired in old adults (Rypma & D'Esposito, 2000). Just as left prefrontal recruitment at baseline may reflect a state more stressed by the effects of age, right superior prefrontal recruitment may represent a state less stressed by the effects of age. Finally, greater posterior cingulate activation during go events related to preserved performance after sleep deprivation (see chapter 4, Table 4.3, Figure 4.2D and F). This activation is rather unintuitive. Posterior cingulate and medial prefrontal activation has generally been associated with the 'default mode' (Gusnard et al., 2001; Raichle et al., 2001). Greater activation within these regions during task performance has been linked to larger age-related performance impairments (Gais et al., 2007; Grady et al., 2006; Persson et al., 2007). However, task-related posterior cingulate activation can relate to internally generated attentional shifts towards externally relevant stimuli based on environmentally presented cues, as is discussed in chapter 1 (Hopfinger et al., 2000; Hopfinger et al., 2001; Mesulam et al., 2001; Small et al., 2003). In study 2's design, a centrally presented spatially uninformative cue was presented before stimuli presentation in the go/no-go task. This cue allowed participants to know that stimuli were about to be presented within 200 to 800 ms. Greater utilization of this cue by old adults may have led to attention being more focused on the task leading to a reduced likelihood of lapsing. Therefore, greater recruitment of posterior cingulate activation in the baseline condition may relate to a greater capacity to focus on task-related attentional cues when sleep-deprived.

These data suggest that the relationship between baseline brain activation and the effects of sleep deprivation on performance depends on task and age. Further, these data suggest that greater baseline activation is not all good. Instead, it depends on which regions are more active at baseline. Young adults who are less able to suppress default mode activity perform more poorly, whereas old adults who rely more on right visuo-motor activity perform more poorly. Greater baseline parietal activation predicted preserved performance in both age groups, though the type of performance preserved depended on age. This suggests a fundamental shift in the way in which old adults perform the same task in a baseline state. This shift alters the way old brains compensate for sleep deprivation and alters how following subsequent sleep brain activity relates to recovered performance.

General conclusions

It is widely held that sleep deprivation impairs performance and alters related brain activity. Yet, how sleep deprivation affects these brain-behavior relationships and how subsequent sleep recovers the brain from these effects remains poorly understood. In the current dissertation, we show that the prefrontal cortex is affected by age and by sleep deprivation, but the prefrontal cortex is not affected alone. Regions important for cognitive control, such as the cingulate and insula, are also affected by both age and sleep deprivation. We show that sleep deprivation alters the way in which brain activation leads to performance, suggesting a change in the functional organization of task performance. This functional re-organization is most likely to relate to a change in

cognitive strategy or a shift in how brain networks support behavior. This, in particular, is important, because if we perform the task differently when sleepy, targeted cognitive training may be able to mitigate the effects of sleep loss on performance. How this reorganization manifests is dependent upon how tasks are performed at baseline, which is affected by age. Thus, the neural response to sleep deprivation and subsequent recovery sleep is also age-dependent. Since the physiology of sleep is also altered with age, the way in which sleep recovers next day brain activation is also dependent upon age. These age-related changes in the neural response to sleep loss and recovery do not necessarily result in worse performance outcomes. However, it is likely these changes reflect a shift in cognitive strategy to maintain performance. Therefore, any attempts to better predict and manage the effects of sleep loss or improve the effects of recovery sleep on daytime function will need to account for age. This is important as any strategies employed to manage sleep loss or manipulate the recovery process may help young adults but may hurt or be unhelpful to old adults. For example, delta power increases during recovery sleep improves performance recovery in young adults, but this relationship does not seem apparent in old adults. Thus, use of transcranial magnetic stimulation or direct current stimulation during sleep to improve delta power may be helpful to young adults but may not be helpful for old adults. Sleep loss is pervasive throughout society, but the effects of sleep loss are not the same in all individuals. In fact, the individual variability in the response to sleep deprivation is rather large (Van Dongen et al., 2007). Better understanding of how sleep loss affects us on an individual basis is critical to the management of sleep loss at a societal level. Aging appears to be a factor at a behavioral

and neural level, and this appears to be so due to baseline differences in how a task is performed at a neural level. Knowing this helps guide us towards a fuller understanding of how age affects the response to sleep deprivation and recovery, and futher informs us as to what alternate strategies may be necessary to manage the effects of sleep loss in old adults.

Future directions

A variety of future directions for research would be valuable in light of the data from this disseration. Some These directions will be addressed below and are discussed separately as relating to the following topics: 1) sleep deprivation and neural network connectivity, 2) recovery sleep and recovery of daytime brain function, 3) effects of sleep loss and age as related to functional reorganization and cognitive strategy shifts, 4) generalizability of sleep deprivation and recovery effects to sleep restriction paradigms, and 5) relationships between lapses and non-lapse brain activity and inhibitory errors.

Sleep deprivation and effective connectivity

We know that age can result in changes in effective connectivity, i.e. the way in which distinct regions of task-related brain activity influence each other (Cabeza, McIntosh et al., 1997). Little is known about how sleep deprivation and the interaction of age and sleep deprivation alters effective connectivity, and how these changes in connectivity relate to performance changes. Cognitive behaviors presumably arise from the interaction between distinct brain regions as part of a series of interacting distributed

networks (Mesulam, 1998). The data from this report, if viewed from the perspective of recent data (Dosenbach et al., 2007), indicate that young and old adults may rely on the functioning of different networks to preserve performance. Specifically, young adults appear to rely on a network of fronto-parietal regions associated with adaptation of cognitive control on a trial by trial basis, whereas old adults may rely on a network of cingulate, insula, and fusiform regions which relate to the maintenance of task mode. Utilization of methods such as dynamic causal modeling (DCM) or graph analysis could be used to determine how sleep deprivation alters interactions between brain regions within a network and alters interactions between distinct networks (Dosenbach et al., 2007; Friston, 2002; Salvador et al., 2005). Relationships could then be obtained between these changes and performance changes. This is an important step towards understanding how brain function is altered by sleep deprivation and how these alterations give rise to performance impairments.

Recovering baseline

The data from this report are among the first to explore the relationships between brain activity following recovery sleep and performance recovery. As far as I am aware, these data are the first to explore the relationships between the spectral properties of night time recovery sleep and daytime task-related brain activity. Further exploration is needed in order to better understand the recovery process and how it relates to behavioral recovery. In the data presented in chapter 3, changes in delta power and sigma power related to changes in task-related brain activity in young and old adults, respectively. Are

these changes regionally specific? Specifically, would regional changes in delta power and sigma power relate to regional changes in task-related brain activity the following day? This question could be explored using Tononi's method of high density EEG recording and analysis (Massimini et al., 2004). Additionally, does improvement of these night time spectral variables lead to improved recovery? Born's group has shown that direct current stimulation of the frontal cortex during sleep within the delta frequency range results in improved episodic memory performance the next day (Marshall et al., 2006; Marshall et al., 2004). The resulting hypothesis was that slow wave sleep improves memory consolidation. However, slow wave sleep may also restore general functioning within the prefrontal cortex. Encoding and retrieval of episodic memories relies upon the prefrontal cortex (Tulving et al., 1994). We demonstrate in chapter 3 that the change in delta power from baseline to recovery sleep is associated with the recovery of right prefrontal activation the next day. It would follow, then, that if Born's methodology were used to improve delta power during the first three hours of recovery sleep, recovery of prefrontal functioning would be enhanced. It would also follow from our data in chapter 3, that this effect may not occur in old adults. These studies would be an important step towards understanding how recovery sleep results in recovered brain activity and related functioning, and how age alters this response.

Sleep deprivation and age: functional reorganization or shift in cognitive strategy?

Age and sleep deprivation both result in changes in brain-behavior relationships, and the data from chapter 4 suggest that the interaction of these two provides different changes. As demonstrated in chapter 1, sleep loss results in a shift in what brain regions are associated with good performance within an individual. This can result from a change in the way the brain performs the same cognitive functions, or from a shift in the cognitive strategy employed to perform the same task. The neuroimaging literature in both the aging and sleep deprivation fields are plagued with studies that cannot reconcile these two possibilities.

Future studies will have to employ the use of tasks that parametrically manipulate distinct perceptual, motor, and cognitive variables within the same adults in rested and sleep-deprived states. If sleep deprivation results simply in a functional reorganization of task performance, then theoretically it should not matter which of these aspects of the task is varied. In all conditions, and in all manipulations, the effects of sleep deprivation on brain activity should be similar. However, if sleep deprivation results in subtle shifts in cognitive strategy towards relying more on certain perceptual, motor, or cognitive abilities, then the effects of sleep deprivation would be different depending on which variable was being manipulated. Any study of this kind would also require thorough debriefing of study subjects in order to determine whether a shift in cognitive strategy was employed on a conscious level, and whether these shifts were consistent or disparate across subjects. These kinds of studies will aid in understanding why these changes in

response to sleep deprivation occur, and this understanding will aid in determining ways in which to improve the management of the effects of sleep loss on performance.

Effects of sleep restriction and subsequent recovery sleep on task-related brain activity

Total sleep deprivation is a generally rare form of sleep loss. A much more common form of sleep loss is a regular restriction of sleep amounts to a shorter than desired period of time (National Sleep Foundation, 2005). Though studies have explored the behavioral consequences of restricted sleep amounts (Belenky et al., 2003; D. F. Dinges et al., 1997; Friedmann et al., 1977; Herscovitch & Broughton, 1981; Herscovitch et al., 1980; Jewett et al., 1999; Jewett & Kronauer, 1999; Van Dongen et al., 2003; Webb & Agnew, 1965, 1974; R.T. Wilkinson, 1969), to date no studies have explored the effects of recurrently restricted sleep on brain activation. This is an important set of studies to conduct, for we do not know whether the effects of acute total sleep deprivation generalize to the effects of recurrently restricted sleep. Further, since rebound sleep can be different following restricted versus totally deprived sleep (W. Dement, 1960; Spiegel et al., 1999; Webb & Agnew, 1965), the effects of recovery sleep on brain function may also differ. These studies will be more able to assess the effects of sleep loss on brain function in a more real world setting.

Lapses and errors of commission: functionally related?

As outlined in the introduction section, I propose that the neurobiology of lapses and errors of commission will differ, but be related. Specifically, as Chee's recent data

show (Chee et al., 2008), lapses that occur after sleep deprivation have a different neurobiological basis than lapses that occur in a rested state. These lapses presumably occur due to an increase in the pressure to sleep which can result in intermittent microsleeps. These microsleeps would also presumably result in the same cortical changes as observed in the transition from wake to NREM sleep states, though perhaps these changes will not be as dramatic. The following hypothesis, then, is that errors of commission occur, because of the intermittent suppression of cortical regions that are required to perform the task. This intermittent suppression would result in reduced processing efficiency and altered effective connectivity even while an individual is awake and responding. Since lateral prefrontal cortex is so affected by sleep deprivation and the transition from wake to NREM sleep states, it is posited that processing efficiency within the prefrontal cortex would be reduced and this would result in an increase in the likelihood to respond inappropriately. This hypothesis could be tested using an EEG-fMRI methodology. Upon the occurrence of microsleep-related lapses, as defined as NREM EEG rhythm intrusion, it would be presumed that certain task-related cortical regions would be suppressed. If my hypothesis is correct, the degree of suppression of these task-related cortical regions during lapses would then presumably predict the likelihood of commission errors and the degree of task-related recruitment on following trials where an individual is awake and responding.

References

Adam, M., Retey, J. V., Khatami, R., & Landolt, H. P. (2006). Age-related changes in the time course of vigilant attention during 40 hours without sleep in men. *Sleep, 29*(1), 55-57.

Agnew, H. W., Jr, Webb, W. B., & Williams, R. L. (1966). The first night effect: an EEG study of sleep. *Psychophysiology, 2*(3), 263-266.

Agnew, H. W., Jr., Webb, W. B., & Williams, R. L. (1964). The Effects of Stage Four Sleep Deprivation. *Electroencephalogr Clin Neurophysiol, 17*, 68-70.

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). The inferential impact of global signal covariates in functional neuroimaging analyses. *Neuroimage, 8*(3), 302-306.

Akerstedt, T., Fredlund, P., Gillberg, M., & Jansson, B. (2002). A prospective study of fatal occupational accidents -- relationship to sleeping difficulties and occupational factors. *J Sleep Res, 11*(1), 69-71.

Almeida, O. P., Tamai, S., & Garrido, R. (1999). Sleep complaints among the elderly: results from a survey in a psychogeriatric outpatient clinic in Brazil. *Int Psychogeriatr, 11*(1), 47-56.

American Academy of Sleep Medicine. (2005). *International classification of sleep disorders: Diagnostic and coding manual* (second ed.). Westchester, IL: American Academy of Sleep Medicine.

Amir, N., Elias, J., Klumpp, H., & Przeworski, A. (2003). Attentional bias to threat in social phobia: facilitated processing of threat or difficulty disengaging attention from threat? *Behav Res Ther, 41*(11), 1325-1335.

Angus, R. G., Heslegrave, R. J., & Myles, W. S. (1985). Effects of prolonged sleep deprivation, with and without chronic physical exercise, on mood and performance. *Psychophysiology, 22*(3), 276-282.

Antle, M. C., & Mistlberger, R. E. (2000). Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. *J Neurosci, 20*(24), 9326-9332.

Aron, A. R., Monsell, S., Sahakian, B. J., & Robbins, T. W. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain, 127*(Pt 7), 1561-1573.

Arrigoni, E., Chamberlin, N. L., Saper, C. B., & McCarley, R. W. (2006). Adenosine inhibits basal forebrain cholinergic and noncholinergic neurons in vitro. *Neuroscience, 140*(2), 403-413.

Aschoff, J. (1965). Circadian Rhythms in Man. *Science, 148*, 1427-1432.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science, 118*(3062), 273-274.

Aston-Jones, G., Chen, S., Zhu, Y., & Oshinsky, M. L. (2001). A neural circuit for circadian regulation of arousal. *Nat Neurosci, 4*(7), 732-738.

Atienza, M., Cantero, J. L., & Stickgold, R. (2004). Posttraining sleep enhances automaticity in perceptual discrimination. *J Cogn Neurosci, 16*(1), 53-64.

Attwell, D., & Iadecola, C. (2002). The neural basis of functional brain imaging signals. *Trends Neurosci, 25*(12), 621-625.

Babkoff, H., French, J., Whitmore, J., & Sutherlin, R. (2002). Single-dose bright light and/or caffeine effect on nocturnal performance. *Aviat Space Environ Med, 73*(4), 341-350.

Backhaus, J., Hoeckesfeld, R., Born, J., Hohagen, F., & Junghanns, K. (2008). Immediate as well as delayed post learning sleep but not wakefulness enhances declarative memory consolidation in children. *Neurobiol Learn Mem, 89*(1), 76-80.

Backman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., et al. (1997). Brain activation in young and older adults during implicit and explicit retrieval. *J Cogn Neurosci, 9*(3), 378-391.

Balsalobre, A., Damiola, F., & Schibler, U. (1998). A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell, 93*(6), 929-937.

Barch, D. M., Sabb, F. W., Carter, C. S., Braver, T. S., Noll, D. C., & Cohen, J. D. (1999). Overt verbal responding during fMRI scanning: empirical investigations of problems and potential solutions. *Neuroimage, 10*(6), 642-657.

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123 (Pt 11)*, 2189-2202.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Arch Gen Psychiatry, 4*, 561-571.

Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., et al. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res, 12*(1), 1-12.

Bell-McGinty, S., Habeck, C., Hilton, H. J., Rakitin, B., Scarmeas, N., Zarahn, E., et al. (2004). Identification and differential vulnerability of a neural network in sleep deprivation. *Cereb Cortex, 14*(5), 496-502.

Bellgrove, M. A., Hester, R., & Garavan, H. (2004). The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia, 42*(14), 1910-1916.

Bentivoglio, M., & Grassi-Zucconi, G. (1997). The pioneering experimental studies on sleep deprivation. *Sleep, 20*(7), 570-576.

Bills, A. G. (1931). Blocking: A new principle of mental fatigue. *American Journal of Psychology, 43*, 230-245.

Biswas, S., Mishra, P., & Mallick, B. N. (2006). Increased apoptosis in rat brain after rapid eye movement sleep loss. *Neuroscience, 142*(2), 315-331.

Bjerner, B. (1949). Alpha depression and lowered pulse rate during delayed actions in a serial reaction test: A study in sleep deprivation. *Acta Physiologica Scandinavica, 19*(suppl. 65), 1-93.

Blagrove, M., Alexander, C., & Horne, J. (1995). The Effects of Chronic Sleep Reduction on the Performance of Cognitive Tasks Sensitive to Sleep Deprivation. *Applied Cognitive Psychology, 9*, 21-40.

Blake, H., & Gerard, R. W. (1937). Brain potentials during sleep. *Am J Physiol, 119*(4), 692-703.

Bliwise, D. L. (1996). Historical change in the report of daytime fatigue. *Sleep, 19*(6), 462-464.

Bonnet, M. H. (1985). Recovery of performance during sleep following sleep deprivation in older normal and insomniac adult males. *Percept Mot Skills, 60*(1), 323-334.

Bonnet, M. H. (1986). Effect of 64 hours of sleep deprivation upon sleep in geriatric normals and insomniacs. *Neurobiol Aging, 7*(2), 89-96.

Bonnet, M. H. (1989). The effect of sleep fragmentation on sleep and performance in younger and older subjects. *Neurobiol Aging, 10*(1), 21-25.

Bonnet, M. H., & Arand, D. L. (1989). Sleep loss in aging. *Clin Geriatr Med, 5*(2), 405-420.

Bonnet, M. H., & Rosa, R. R. (1987). Sleep and performance in young adults and older normals and insomniacs during acute sleep loss and recovery. *Biol Psychol, 25*(2), 153-172.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., et al. (2003). Neural development of selective attention and response inhibition. *Neuroimage, 20*(2), 737-751.

Borbely, A. A. (1982). A two process model of sleep regulation. *Hum Neurobiol, 1*(3), 195-204.

Borbely, A. A., Baumann, F., Brandeis, D., Strauch, I., & Lehmann, D. (1981). Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol, 51*(5), 483-495.

Born, J., Rasch, B., & Gais, S. (2006). Sleep to remember. *Neuroscientist, 12*(5), 410-424.

Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain, 120 (Pt 7)*, 1173-1197.

Brett, M., Anton, J. L., Valabregue, R., & Poline, J. B. (2002). *Region of interest analysis using an SPM toolbox [abstract]*. Paper presented at the 8th International Conference on Functional Mapping of the Human Brain.

Buchsbaum, B. R., Greer, S., Chang, W. L., & Berman, K. F. (2005). Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum Brain Mapp, 25*(1), 35-45.

Buckner, R. L., Snyder, A. Z., Sanders, A. L., Raichle, M. E., & Morris, J. C. (2000). Functional brain imaging of young, nondemented, and demented older adults. *J Cogn Neurosci, 12 Suppl 2*, 24-34.

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: default activity and spontaneous network correlations. *Neuroimage, 37*(4), 1091-1096; discussion 1097-1099.

Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain, 124*(Pt 10), 2074-2086.

Burock, M. A., Buckner, R. L., Woldorff, M. G., Rosen, B. R., & Dale, A. M. (1998). Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. *NeuroReport, 9*, 3735-3739.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci, 4*(6), 215-222.

Butler, S., & Smith, C. (1981). Brief PS and retardation of learning performance. *Sleep Res, 10*, 125.

Buysse, D. J., Barzansky, B., Dinges, D., Hogan, E., Hunt, C. E., Owens, J., et al. (2003). Sleep, fatigue, and medical training: setting an agenda for optimal learning and patient care. *Sleep, 26*(2), 218-225.

Buysse, D. J., Nofzinger, E. A., Germain, A., Meltzer, C. C., Wood, A., Ombao, H., et al. (2004). Regional brain glucose metabolism during morning and evening wakefulness in humans: preliminary findings. *Sleep, 27*(7), 1245-1254.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213.

Buzsaki, G. (1996). The hippocampo-neocortical dialogue. *Cereb Cortex, 6*(2), 81-92.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Houle, S., Mangels, J. A., & Nyberg, L. (2000). Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study. *J Cogn Neurosci, 12*(1), 197-206.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *J Neurosci, 17*(1), 391-400.

Cabeza, R., McIntosh, A. R., Tulving, E., Nyberg, L., & Grady, C. L. (1997). Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport, 8*(16), 3479-3483.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci, 12*(1), 1-47.

Caldwell, J. A., Mu, Q., Smith, J. K., Mishory, A., Caldwell, J. L., Peters, G., et al. (2005). Are individual differences in fatigue vulnerability related to baseline differences in cortical activation? *Behav Neurosci, 119*(3), 694-707.

Campbell, S. S., & Tobler, I. (1984). Animal sleep: a review of sleep duration across phylogeny. *Neurosci Biobehav Rev, 8*(3), 269-300.

Campbell, S. S., & Zulley, J. (1989). Evidence for circadian influence on human slow wave sleep during daytime sleep episodes. *Psychophysiology, 26*(5), 580-585.

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *J Neurosci, 20*(19), RC99.

Carskadon, M. A., & Dement, W. (1994). Normal Human Sleep: An Overview. In M. H. Kryger, T. Roth & W. Dement (Eds.), *Principles and Practice of Sleep Medicine* (second ed., pp. 16-25). Philadelphia: W.B. Saunders Company.

Carskadon, M. A., & Dement, W. C. (1980). Distribution of REM sleep on a 90 minute sleep-wake schedule. *Sleep, 2*(3), 309-317.

Carskadon, M. A., & Dement, W. C. (1985). Sleep loss in elderly volunteers. *Sleep, 8*(3), 207-221.

Chao, L. L., & Knight, R. T. (1997). Prefrontal deficits in attention and inhibitory control with aging. *Cereb Cortex, 7*(1), 63-69.

Chee, M. W., & Choo, W. C. (2004). Functional imaging of working memory after 24 hr of total sleep deprivation. *J Neurosci, 24*(19), 4560-4567.

Chee, M. W., Chuah, L. Y., Venkatraman, V., Chan, W. Y., Philip, P., & Dinges, D. F. (2006). Functional imaging of working memory following normal sleep and after 24 and 35 h of sleep deprivation: Correlations of fronto-parietal activation with performance. *Neuroimage, 31*(1), 419-428.

Chee, M. W., & Chuah, Y. M. (2007). Functional neuroimaging and behavioral correlates of capacity decline in visual short-term memory after sleep deprivation. *Proc Natl Acad Sci U S A, 104*(22), 9487-9492.

Chee, M. W., Tan, J. C., Zheng, H., Parimal, S., Weissman, D. H., Zagorodnov, V., et al. (2008). Lapsing during sleep deprivation is associated with distributed changes in brain activation. *J Neurosci, 28*(21), 5519-5528.

Chemelli, R. M., Willie, J. T., Sinton, C. M., Elmquist, J. K., Scammell, T., Lee, C., et al. (1999). Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell, 98*(4), 437-451.

Choo, W. C., Lee, W. W., Venkatraman, V., Sheu, F. S., & Chee, M. W. (2005). Dissociation of cortical regions modulated by both working memory load and sleep deprivation and by sleep deprivation alone. *Neuroimage, 25*(2), 579-587.

Chou, T. C., Bjorkum, A. A., Gaus, S. E., Lu, J., Scammell, T. E., & Saper, C. B. (2002). Afferents to the ventrolateral preoptic nucleus. *J Neurosci, 22*(3), 977-990.

Chou, T. C., Scammell, T. E., Gooley, J. J., Gaus, S. E., Saper, C. B., & Lu, J. (2003). Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J Neurosci, 23*(33), 10691-10702.

Chuah, Y. M., Venkatraman, V., Dinges, D. F., & Chee, M. W. (2006). The neural basis of interindividual variability in inhibitory efficiency after sleep deprivation. *J Neurosci, 26*(27), 7156-7162.

Cirelli, C., Faraguna, U., & Tononi, G. (2006). Changes in brain gene expression after long-term sleep deprivation. *J Neurochem, 98*(5), 1632-1645.

Cirelli, C., Gutierrez, C. M., & Tononi, G. (2004). Extensive and divergent effects of sleep and wakefulness on brain gene expression. *Neuron, 41*(1), 35-43.

Cirelli, C., Shaw, P. J., Rechtschaffen, A., & Tononi, G. (1999). No evidence of brain cell degeneration after long-term sleep deprivation in rats. *Brain Res, 840*(1-2), 184-193.

Cirelli, C., & Tononi, G. (2000). Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J Neurosci, 20*(24), 9187-9194.

Cohen, G. (1988). Age differences in memory for texts: Production deficiency or processing limitations? In L. D. Burke (Ed.), *Language, memory and aging* (pp. 171-190). Cambridge, England: Cambridge University Press.

Collette, F., Van der Linden, M., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2001). The functional anatomy of inhibition processes investigated with the Hayling task. *Neuroimage, 14*(2), 258-267.

Constantinidis, C., & Steinmetz, M. A. (2001). Neuronal responses in area 7a to multiple stimulus displays: II. responses are suppressed at the cued location. *Cereb Cortex, 11*(7), 592-597.

Contreras, D., & Steriade, M. (1995). Cellular basis of EEG slow rhythms: a study of dynamic corticothalamic relationships. *J Neurosci, 15*(1 Pt 2), 604-622.

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., et al. (1998). A common network of functional areas for attention and eye movements. *Neuron, 21*(4), 761-773.

Corbetta, M., Miezin, F. M., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *J Neurosci, 13*(3), 1202-1226.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215.

Coull, J. T. (1998). Neural correlates of attention and arousal: insights from electrophysiology, functional neuroimaging and psychopharmacology. *Prog Neurobiol, 55*(4), 343-361.

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Phil Trans R Soc Lond B Biol Sci, 302*, 341-359.

Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol, 493*(1), 154-166.

Crivello, N. A., Rosenberg, I. H., Dallal, G. E., Bielinski, D., & Joseph, J. A. (2005). Age-related changes in neutral sphingomyelin-specific phospholipase C activity in striatum, hippocampus, and frontal cortex: implication for sensitivity to stress and inflammation. *Neurochem Int, 47*(8), 573-579.

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., Brown, E. N., Mitchell, J. F., Rimmer, D. W., et al. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science, 284*(5423), 2177-2181.

Czeisler, C. A., Dumont, M., Duffy, J. F., Steinberg, J. D., Richardson, G. S., Brown, E. N., et al. (1992). Association of sleep-wake habits in older people with changes in output of circadian pacemaker. *Lancet, 340*(8825), 933-936.

Czeisler, C. A., & Guilleminault, C. (1979). 250 years ago: tribute to a new discipline (1729--1979). *Sleep, 2*(2), 155-160.

Czeisler, C. A., Weitzman, E., Moore-Ede, M. C., Zimmerman, J. C., & Knauer, R. S. (1980). Human sleep: its duration and organization depend on its circadian phase. *Science, 210*(4475), 1264-1267.

Czisch, M., Wehrle, R., Kaufmann, C., Wetter, T. C., Holsboer, F., Pollmacher, T., et al. (2004). Functional MRI during sleep: BOLD signal decreases and their electrophysiological correlates. *Eur J Neurosci, 20*(2), 566-574.

D'Esposito, M., Zarahn, E., Aguirre, G. K., & Rypma, B. (1999). The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage, 10*(1), 6-14.

Dave, A. S., & Margoliash, D. (2000). Song replay during sleep and computational rules for sensorimotor vocal learning. *Science, 290*(5492), 812-816.

Dave, A. S., Yu, A. C., & Margoliash, D. (1998). Behavioral state modulation of auditory activity in a vocal motor system. *Science, 282*(5397), 2250-2254.

Dawson, D., & Reid, K. (1997). Fatigue, alcohol and performance impairment. *Nature, 388*(6639), 235.

Dawson, D., & Zee, P. (2005). Work hours and reducing fatigue-related risk: good research vs good policy. *Jama, 294*(9), 1104-1106.

de Gonzaga Gawryszewski, L., Riggio, L., Rizzolatti, G., & Umilta, C. (1987). Movements of attention in the three spatial dimensions and the meaning of "neutral" cues. *Neuropsychologia, 25*(1A), 19-29.

De Manaceine, M. (1894). Quelques observations experimentales sur l'influence de l'insomnie absolue. *Arch Ital Biol, 21*, 322-325.

de Zubicaray, G. I., Andrew, C., Zelaya, F. O., Williams, S. C., & Dumanoir, C. (2000). Motor response suppression and the prepotent tendency to respond: a parametric fMRI study. *Neuropsychologia, 38*(9), 1280-1291.

Deboer, T., Vansteensel, M. J., Detari, L., & Meijer, J. H. (2003). Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci, 6*(10), 1086-1090.

Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychol Sci, 5*, 303-305.

Della-Maggiore, V., Sekuler, A. B., Grady, C. L., Bennett, P. J., Sekuler, R., & McIntosh, A. R. (2000). Corticolimbic interactions associated with performance on a short-term memory task are modified by age. *J Neurosci, 20*(22), 8410-8416.

Dement, W. (1960). The effect of dream deprivation. *Science, 131*, 1705-1707.

Dement, W. C., & Vaughan, C. (1999). *The Promise of Sleep: A Pioneer in Sleep Medicine Explores the Vital Connection Between Health, Happiness, and a Good Night's Sleep*. New York: Dell.

Denisova, N. A., Shukitt-Hale, B., Rabin, B. M., & Joseph, J. A. (2002). Brain signaling and behavioral responses induced by exposure to (56)Fe-particle radiation. *Radiat Res, 158*(6), 725-734.

Dickman, M. S. (2001). von Economo encephalitis. *Arch Neurol, 58*(10), 1696-1698.

Dijk, D. J., Beersma, D. G., & van den Hoofdakker, R. H. (1989). All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. *Neurobiol Aging, 10*(6), 677-682.

Dijk, D. J., & Czeisler, C. A. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci, 15*(5 Pt 1), 3526-3538.

Dijk, D. J., Hayes, B., & Czeisler, C. A. (1993). Dynamics of electroencephalographic sleep spindles and slow wave activity in men: effect of sleep deprivation. *Brain Res, 626*(1-2), 190-199.

Dinges, D., & Kribbs, N. (1991). Chapter 4 - Performing while sleepy: effects of experimentally-induced sleepiness. In T. H. Monk (Ed.), *Sleep, Sleepiness and Performance.* (pp. 97-128). New York: John Wiley & Sons.

Dinges, D., & Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Beh Res Meth, Instr, Comp, 17*, 652-655.

Dinges, D. F. (1995). An overview of sleepiness and accidents. *J Sleep Res, 4*(S2), 4-14.

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep, 20*(4), 267-277.

Doran, S. M., Van Dongen, H. P., & Dinges, D. (2001). Sustained attention performance during sleep deprivation: evidence of state-instability. *Arch Ital Biol, 139*(3), 253-267.

Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., et al. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A, 104*(26), 11073-11078.

Drosopoulos, S., Wagner, U., & Born, J. (2005). Sleep enhances explicit recollection in recognition memory. *Learn Mem, 12*(1), 44-51.

Drummond, S. P., Bischoff-Grethe, A., Dinges, D. F., Ayalon, L., Mednick, S. C., & Meloy, M. J. (2005). The neural basis of the psychomotor vigilance task. *Sleep, 28*(9), 1059-1068.

Drummond, S. P., & Brown, G. G. (2001). The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharmacology, 25*(5 Suppl), S68-73.

Drummond, S. P., Brown, G. G., Gillin, J. C., Stricker, J. L., Wong, E. C., & Buxton, R. B. (2000). Altered brain response to verbal learning following sleep deprivation. *Nature, 403*(6770), 655-657.

Drummond, S. P., Brown, G. G., Salamat, J. S., & Gillin, J. C. (2004). Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep, 27*(3), 445-451.

Drummond, S. P., Brown, G. G., Stricker, J. L., Buxton, R. B., Wong, E. C., & Gillin, J. C. (1999). Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *Neuroreport, 10*(18), 3745-3748.

Drummond, S. P., Gillin, J. C., & Brown, G. G. (2001). Increased cerebral response during a divided attention task following sleep deprivation. *J Sleep Res, 10*(2), 85-92.

Drummond, S. P., Meloy, M. J., Yanagi, M. A., Orff, H. J., & Brown, G. G. (2005). Compensatory recruitment after sleep deprivation and the relationship with performance. *Psychiatry Res, 140*(3), 211-223.

Drummond, S. P., Salamat, J. S., Yanagi, M. A., Stiller, C., Chen, T., & Orff, H. J. (2005). Sleep Deprivation Affects Inhibitory Ability. *Sleep, 28*(Abstract Supplement), A132.

Dunlap, J. C. (1999). Molecular bases for circadian clocks. *Cell, 96*(2), 271-290.

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Semin Neurol, 25*(1), 117-129.

Duverne, S., Motamedinia, S., & Rugg, M. D. (2008). The relationship between aging, performance, and the neural correlates of successful memory encoding. *Cereb Cortex*.

Ebisawa, T., Uchiyama, M., Kajimura, N., Mishima, K., Kamei, Y., Katoh, M., et al. (2001). Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. *EMBO Rep, 2*(4), 342-346.

Eichele, T., Debener, S., Calhoun, V. D., Specht, K., Engel, A. K., Hugdahl, K., et al. (2008). Prediction of human errors by maladaptive changes in event-related brain networks. *Proc Natl Acad Sci U S A, 105*(16), 6173-6178.

Elkin, A. J., & Murray, D. J. (1974). The effects of sleep loss on short-term recognition memory. *Canadian Journal of Psychology, 28*(2), 192-198.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2001). Changes of error-related ERPs with age. *Exp Brain Res, 138*(2), 258-262.

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *Neuroimage, 26*(2), 471-479.

Feinberg, I., & Carlson, V. R. (1968). Sleep variables as a function of age in man. *Arch Gen Psychiat, 18*, 239-250.

Feldman, M. J., & Drasgow, J. (1959). *The Visual-Verbal Test*. Los Angeles, CA: Los Angeles: Western Psychological Services.

Fenn, K. M., Nusbaum, H. C., & Margoliash, D. (2003). Consolidation during sleep of perceptual learning of spoken language. *Nature, 425*(6958), 614-616.

Filley, C. M., & Cullum, C. M. (1994). Attention and vigilance functions in normal aging. *Appl Neuropsychol, 1*(1-2), 29-32.

Fischer, S., Hallschmid, M., Elsner, A. L., & Born, J. (2002). Sleep forms memory for finger skills. *Proc Natl Acad Sci U S A, 99*(18), 11987-11991.

Fischer, S., Nitschke, M. F., Melchert, U. H., Erdmann, C., & Born, J. (2005). Motor memory consolidation in sleep shapes more effective neuronal representations. *J Neurosci, 25*(49), 11248-11255.

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B., & Blazer, D. G. (1995). Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep, 18*(6), 425-432.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189-198.

Fransen, M., Wilsmore, B., Winstanley, J., Woodward, M., Grunstein, R., Ameratunga, S., et al. (2006). Shift work and work injury in the New Zealand Blood Donors' Health Study. *Occup Environ Med, 63*(5), 352-358.

Frey, D. J., Badia, P., & Wright, K. P., Jr. (2004). Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *J Sleep Res, 13*(4), 305-315.

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *J Exp Psychol Gen, 133*(1), 101-135.

Friedmann, J. K., Globus, G. G., Huntley, A., Mullaney, D. J., Naitoh, P., & Johnson, L. C. (1977). Performance and Mood During and After Gradual Sleep Reduction. *Psychophysiology, 14*(3), 245-250.

Friston, K. J. (2002). Bayesian estimation of dynamical systems: an application to fMRI. *Neuroimage, 16*(2), 513-530.

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., & Frith, C. D. (1996). Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage, 4*(3 Pt 1), 223-235.

Froberg, J. E. (1977). Twenty-four-hour patterns in human performance, subjective and physiological variables and differences between morning and evening active subjects. *Biol Psychol, 5*(2), 119-134.

Fuller, P. M., Saper, C. B., & Lu, J. (2007). The pontine REM switch: past and present. *J Physiol, 584*(Pt 3), 735-741.

Gais, S., Albouy, G., Boly, M., Dang-Vu, T. T., Darsaud, A., Desseilles, M., et al. (2007). Sleep transforms the cerebral trace of declarative memories. *Proc Natl Acad Sci U S A, 104*(47), 18778-18783.

Gais, S., Molle, M., Helms, K., & Born, J. (2002). Learning-dependent increases in sleep spindle density. *J Neurosci, 22*(15), 6830-6834.

Gais, S., Plihal, W., Wagner, U., & Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. *Nat Neurosci, 3*(12), 1335-1339.

Garavan, H., Ross, T. J., Murphy, K., Roche, R. A., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage, 17*(4), 1820-1829.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proc Natl Acad Sci U S A, 96*(14), 8301-8306.

Gekakis, N., Staknis, D., Nguyen, H. B., Davis, F. C., Wilsbacher, L. D., King, D. P., et al. (1998). Role of the CLOCK protein in the mammalian circadian mechanism. *Science, 280*(5369), 1564-1569.

Gitelman, D. R., Nobre, A. C., Parrish, T. B., LaBar, K. S., Kim, Y. H., Meyer, J. R., et al. (1999). A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. *Brain, 122 (Pt 6)*, 1093-1106.

Glisky, E. L., Polster, M. R., & Routhieaux, B. C. (1995). Double dissociation between item and source memory. *Neuropsychology, 9*(2), 229-235.

Gosselin, A., De Koninck, J., & Campbell, K. B. (2005). Total sleep deprivation and novelty processing: implications for frontal lobe functioning. *Clin Neurophysiol, 116*(1), 211-222.

Gottlieb, J. P., Kusunoki, M., & Goldberg, M. E. (1998). The representation of visual salience in monkey parietal cortex. *Nature, 391*(6666), 481-484.

Grady, C. L. (1998). Brain imaging and age-related changes in cognition. *Exp Gerontol, 33*(7-8), 661-673.

Grady, C. L., McIntosh, A. R., Bookstein, F., Horwitz, B., Rapoport, S. I., & Haxby, J. V. (1998). Age-related changes in regional cerebral blood flow during working memory for faces. *Neuroimage, 8*(4), 409-425.

Grady, C. L., McIntosh, A. R., Horwitz, B., Maisog, J. M., Ungerleider, L. G., Mentis, M. J., et al. (1995). Age-related reductions in human recognition memory due to impaired encoding. *Science, 269*(5221), 218-221.

Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R., & Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *J Cogn Neurosci, 18*(2), 227-241.

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Prog Neurobiol*.

Green, D. M., & Swets, J. A. (1966). *Signal Detection Theory and Psychophysics.* New York City: Wiley.

Grutzendler, J., Kasthuri, N., & Gan, W. B. (2002). Long-term dendritic spine stability in the adult cortex. *Nature, 420*(6917), 812-816.

Gulevich, G., Dement, W., & Johnson, L. (1966). Psychiatric and EEG observations on a case of prolonged (264 hours) wakefulness. *Arch Gen Psychiatry, 15*(1), 29-35.

Gunter, T. C., van der Zande, R. D., Wiethoff, M., Mulder, G., & Mulder, L. J. (1987). Visual selective attention during meaningful noise and after sleep deprivation. *Electroencephalogr Clin Neurophysiol Suppl, 40*, 99-107.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A, 98*(7), 4259-4264.

Gvilia, I., Xu, F., McGinty, D., & Szymusiak, R. (2006). Homeostatic regulation of sleep: a role for preoptic area neurons. *J Neurosci, 26*(37), 9426-9433.

Habeck, C., Rakitin, B. C., Moeller, J., Scarmeas, N., Zarahn, E., Brown, T., et al. (2004). An event-related fMRI study of the neurobehavioral impact of sleep deprivation on performance of a delayed-match-to-sample task. *Brain Res Cogn Brain Res, 18*(3), 306-321.

Hammond, W. A. (1865). On sleep and insomnia. *New York Medical Journal, 1*(2), 89-101.

Harrison, Y., & Horne, J. (1998). Sleep loss affects risk-taking. *Journal of Sleep Research, 7*(S2), 113.

Harrison, Y., & Horne, J. A. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *J Sleep Res, 7*(2), 95-100.

Harrison, Y., & Horne, J. A. (1999). One Night of Sleep Loss Impairs Innovative Thinking and Flexible Decision Making. *Organ Behav Hum Decis Process, 78*(2), 128-145.

Harrison, Y., & Horne, J. A. (2000a). The impact of sleep deprivation on decision making: a review. *J Exp Psychol Appl, 6*(3), 236-249.

Harrison, Y., & Horne, J. A. (2000b). Sleep loss and temporal memory. *Q J Exp Psychol A, 53*(1), 271-279.

Harrison, Y., Horne, J. A., & Rothwell, A. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults--a model for healthy aging? *Sleep, 23*(8), 1067-1073.

Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Bower (Ed.), *The Psychology of Learning and Motivation* (Vol. 22, pp. 193-225). New York: Academic Press.

Hayasaka, S., Phan, K. L., Liberzon, I., Worsley, K. J., & Nichols, T. E. (2004). Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage, 22*(2), 676-687.

Hebb, D. O. (1949). *The Organization of Behavior; a Neuropsychological Theory*. New York: Wiley.

Heekeren, H. R., Marrett, S., Bandettini, P. A., & Ungerleider, L. G. (2004). A general mechanism for perceptual decision-making in the human brain. *Nature, 431*(7010), 859-862.

Heekeren, H. R., Marrett, S., Ruff, D. A., Bandettini, P. A., & Ungerleider, L. G. (2006). Involvement of human left dorsolateral prefrontal cortex in perceptual decision making is independent of response modality. *Proc Natl Acad Sci U S A, 103*(26), 10023-10028.

Hendricks, J. C., & Sehgal, A. (2004). Why a fly? Using Drosophila to understand the genetics of circadian rhythms and sleep. *Sleep, 27*(2), 334-342.

Herscovitch, J., & Broughton, R. (1981). Performance deficits following short-term partial sleep deprivation and subsequent recovery oversleeping. *Can J Psychol, 35*(4), 309-322.

Herscovitch, J., Stuss, D., & Broughton, R. (1980). Changes in Cognitive Processing Following Short-term Cumulative Partial Sleep Deprivation and Recovery Oversleeping. *Journal of Clinical Neuropsychology, 2*(4), 301-319.

Heslegrave, R. J., & Angus, R. G. (1985). The effects of task duration and work-session location on performance degradation induced by sleep loss and sustained cognitive work. *Behavior Research Methods, Instruments, and Computers, 17*(6), 592-603.

Hester, R., D'Esposito, M., Cole, M. W., & Garavan, H. (2007). Neural mechanisms for response selection: comparing selection of responses and items from working memory. *Neuroimage, 34*(1), 446-454.

Hester, R. L., Murphy, K., Foxe, J. J., Foxe, D. M., Javitt, D. C., & Garavan, H. (2004). Predicting success: patterns of cortical activation and deactivation prior to response inhibition. *J Cogn Neurosci, 16*(5), 776-785.

Heuninckx, S., Wenderoth, N., Debaere, F., Peeters, R., & Swinnen, S. P. (2005). Neural basis of aging: the penetration of cognition into action control. *J Neurosci, 25*(29), 6787-6796.

Hobson, J. A., Pace-Schott, E. F., & Stickgold, R. (2000). Dreaming and the brain: toward a cognitive neuroscience of conscious states. *Behav Brain Sci, 23*(6), 793-842; discussion 904-1121.

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nat Neurosci, 3*(3), 284-291.

Hopfinger, J. B., Woldorff, M. G., Fletcher, E. M., & Mangun, G. R. (2001). Dissociating top-down attentional control from selective perception and action. *Neuropsychologia, 39*(12), 1277-1291.

Horn, N. R., Dolan, M., Elliott, R., Deakin, J. F., & Woodruff, P. W. (2003). Response inhibition and impulsivity: an fMRI study. *Neuropsychologia, 41*(14), 1959-1966.

Horne, J. (1988). *Why We Sleep: The functions of sleep in humans and other mammals*. New York: Oxford University Press.

Horne, J., & Reyner, L. (1999). Vehicle accidents related to sleep: a review. *Occup Environ Med, 56*(5), 289-294.

Horne, J. A. (1988). Sleep loss and "divergent" thinking ability. *Sleep, 11*(6), 528-536.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol, 4*(2), 97-110.

Horne, J. A., & Reyner, L. A. (1995). Driver sleepiness. *J Sleep Res, 4*(S2), 23-29.

How, J. M., Foo, S. C., Low, E., Wong, T. M., Vijayan, A., Siew, M. G., et al. (1994). Effects of sleep deprivation on performance of Naval seamen: I. Total sleep deprivation on performance. *Ann Acad Med Singapore, 23*(5), 669-675.

Howell, W. H. (1913). Scientific Books: Le probleme physiologique du Sommeil. *Science, 37*(953), 525-526.

Huber, R., Ghilardi, M. F., Massimini, M., Ferrarelli, F., Riedner, B. A., Peterson, M. J., et al. (2006). Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci, 9*(9), 1169-1176.

Huber, R., Ghilardi, M. F., Massimini, M., & Tononi, G. (2004). Local sleep and learning. *Nature, 430*(6995), 78-81.

Huettel, S. A., Singerman, J. D., & McCarthy, G. (2001). The effects of aging upon the hemodynamic response measured by functional MRI. *Neuroimage, 13*(1), 161-175.

Hull, J. T., Wright, K. P., Jr., & Czeisler, C. A. (2003). The influence of subjective alertness and motivation on human performance independent of circadian and homeostatic regulation. *J Biol Rhythms, 18*(4), 329-338.

Inoue, S., Honda, K., & Komoda, Y. (1995). Sleep as neuronal detoxification and restitution. *Behav Brain Res, 69*(1-2), 91-96.

Inouye, S. T., & Kawamura, H. (1979). Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. *Proc Natl Acad Sci U S A, 76*(11), 5962-5966.

Isella, V., Mapelli, C., Morielli, N., Pelati, O., Franceschi, M., & Appollonio, I. M. (2008). Age-related quantitative and qualitative changes in decision making ability. *Behav Neurol, 19*(1-2), 59-63.

James, W. (1890). Chapter X: The consciousness of Self. In *The principles of Psychology*. Holt, New York.

Jewett, M. E., Dijk, D. J., Kronauer, R. E., & Dinges, D. F. (1999). Dose-response relationship between sleep duration and human psychomotor vigilance and subjective alertness. *Sleep, 22*(2), 171-179.

Jewett, M. E., & Kronauer, R. E. (1999). Interactive mathematical models of subjective alertness and cognitive throughput in humans. *J Biol Rhythms, 14*(6), 588-597.

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep, 14*(6), 540-545.

Johnson, L. C., & MacLeod, W. L. (1973). Sleep and awake behavior during gradual sleep reduction. *Percept Mot Skills, 36*(1), 87-97.

Johnson, L. C., Slye, E. S., & Dement, W. (1965). Electroencephalographic and autonomic activity during and after prolonged sleep deprivation. *Psychosom Med, 27*(5), 415-423.

Jongen, E. M., Smulders, F. T., & van Breukelen, G. J. (2006). Varieties of attention in neutral trials: linking RT to ERPs and EEG frequencies. *Psychophysiology, 43*(1), 113-125.

Jouvet, M. (1969). Biogenic amines and the states of sleep. *Science, 163*(862), 32-41.

Jouvet, M., & Michel, F. (1959). [Electromyographic correlations of sleep in the chronic decorticate & mesencephalic cat.]. *C R Seances Soc Biol Fil, 153*(3), 422-425.

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., & Killgore, W. D. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Med, 8*(3), 215-221.

Kales, A., Tan, T. L., Kollar, E. J., Naitoh, P., Preston, T. A., & Malmstrom, E. J. (1970). Sleep patterns following 205 hours of sleep deprivation. *Psychosom Med, 32*(2), 189-200.

Kales, A., Wilson, T., Kales, J. D., Jacobson, A., Paulson, M. J., Kollar, E., et al. (1967). Measurements of all-night sleep in normal elderly persons: effects of aging. *J Am Geriatr Soc, 15*(5), 405-414.

Karni, A., & Sagi, D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. *Proc Natl Acad Sci U S A, 88*(11), 4966-4970.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. *Science, 265*(5172), 679-682.

Karni, A., Weisberg, J., Lalonde, F., & Ungerleider, L. G. (1996). Slow changes in primary and secondary visual cortex associated with perceptual skill learning: an fMRI study. *Neuroimage, 3*, S543.

Kaufmann, C., Wehrle, R., Wetter, T. C., Holsboer, F., Auer, D. P., Pollmacher, T., et al. (2006). Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. *Brain, 129*(Pt 3), 655-667.

Kausler, D. H., & Hakami, M. K. (1982). Frequency judgments by young and elderly adults for relevant stimuli with simultaneously present irrelevant stimuli. *J Gerontol, 37*(4), 438-442.

Kelly, A. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *Neuroimage, 39*(1), 527-537.

Kerkhofs, M., & Lavie, P. (2000). Frederic Bremer 1892-1982: a pioneer in sleep research. *Sleep Med Rev, 4*(5), 505-514.

Killgore, W. D., Balkin, T. J., & Wesensten, N. J. (2006). Impaired decision making following 49 h of sleep deprivation. *J Sleep Res, 15*(1), 7-13.

Kleitman, N. (1963). *Sleep and Wakefulness*. Chicago: University of Chicago Press.

Knipling, R. R., & Wang, J. S. (1994). *Research Note: Crashes and Fatalities Related to Driver Drowsiness/Fatigue*. Washington, D.C.: National Highway Traffic Safety Administration.

Knott, G. W., Quairiaux, C., Genoud, C., & Welker, E. (2002). Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron, 34*(2), 265-273.

Ko, C. H., & Takahashi, J. S. (2006). Molecular components of the mammalian circadian clock. *Hum Mol Genet, 15 Spec No 2*, R271-277.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain, 122 (Pt 5)*, 981-991.

Kryger, M. H., Roth, T., & Dement, W. C. (Eds.). (1994). *Principles and Practices of Sleep Medicine* (Second ed.). Philadelphia: W.B. Saunders Company.

Kubler, A., Murphy, K., Kaufman, J., Stein, E. A., & Garavan, H. (2003). Co-ordination within and between verbal and visuospatial working memory: network modulation and anterior frontal recruitment. *Neuroimage, 20*(2), 1298-1308.

Kubota, K. (1989). Kuniomi Ishimori and the first discovery of sleep-inducing substances in the brain. *Neurosci Res, 6*(6), 497-518.

Kuriyama, K., Stickgold, R., & Walker, M. P. (2004). Sleep-dependent learning and motor-skill complexity. *Learn Mem, 11*(6), 705-713.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. (1999). Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage, 10*(6), 695-704.

Langenecker, S. A., & Nielson, K. A. (2003). Frontal recruitment during response inhibition in older adults replicated with fMRI. *Neuroimage, 20*(2), 1384-1392.

Laurens, K. R., Kiehl, K. A., & Liddle, P. F. (2005). A supramodal limbic-paralimbic-neocortical network supports goal-directed stimulus processing. *Hum Brain Mapp, 24*(1), 35-49.

Laureys, S., Peigneux, P., Phillips, C., Fuchs, S., Degueldre, C., Aerts, J., et al. (2001). Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep. *Neuroscience, 105*(3), 521-525.

Lavie, P. (1987). Ultrashort sleep-wake cycle: timing of REM sleep. Evidence for sleep-dependent and sleep-independent components of the REM cycle. *Sleep, 10*(1), 62-68.

Lee, B. T., Seong Whi, C., Hyung Soo, K., Lee, B. C., Choi, I. G., Lyoo, I. K., et al. (2007). The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry, 31*(7), 1487-1492.

Leger, D. (1994). The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep, 17*(1), 84-93.

Leproult, R., Colecchia, E. F., Berardi, A. M., Stickgold, R., Kosslyn, S. M., & Van Cauter, E. (2003). Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. *Am J Physiol Regul Integr Comp Physiol, 284*(2), R280-290.

Leproult, R., Copinschi, G., Buxton, O., & Van Cauter, E. (1997). Sleep loss results in an elevation of cortisol levels the next evening. *Sleep, 20*(10), 865-870.

Lim, J., Choo, W. C., & Chee, M. W. (2007). Reproducibility of changes in behaviour and fMRI activation associated with sleep deprivation in a working memory task. *Sleep, 30*(1), 61-70.

Lin, L., Faraco, J., Li, R., Kadotani, H., Rogers, W., Lin, X., et al. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell, 98*(3), 365-376.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150-157.

Logothetis, N. K., & Pfeuffer, J. (2004). On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging, 22*(10), 1517-1531.

Loh, S., Lamond, N., Dorrian, J., Roach, G., & Dawson, D. (2004). The validity of psychomotor vigilance tasks of less than 10-minute duration. *Behav Res Methods Instrum Comput, 36*(2), 339-346.

Loomis, A. L., Harvey, E. N., & Hobart, G. A., III. (1937). Cerebral states during sleep, as studied by human brain potentials. *J Exp Psychol, 21*(2), 127-144.

Lu, J., Sherman, D., Devor, M., & Saper, C. B. (2006). A putative flip-flop switch for control of REM sleep. *Nature, 441*(7093), 589-594.

Lu, S. T., Kajola, M., Joutsiniemi, S. L., Knuutila, J., & Hari, R. (1992). Generator sites of spontaneous MEG activity during sleep. *Electroencephalogr Clin Neurophysiol, 82*(3), 182-196.

Luber, B., Stanford, A. D., Bulow, P., Nguyen, T., Rakitin, B. C., Habeck, C., et al. (2008). Remediation of Sleep-Deprivation-Induced Working Memory Impairment with fMRI-Guided Transcranial Magnetic Stimulation. *Cereb Cortex*.

Luria, A. R. (1965). Two kinds of motor perseveration in massive injury of the frontal lobes. *Brain, 88*(1), 1-10.

Lyznicki, J. M., Doege, T. C., Davis, R. M., & Williams, M. A. (1998). Sleepiness, driving, and motor vehicle crashes. Council on Scientific Affairs, American Medical Association. *Jama, 279*(23), 1908-1913.

Macey, P. M., Macey, K. E., Kumar, R., & Harper, R. M. (2004). A method for removal of global effects from fMRI time series. *Neuroimage, 22*(1), 360-366.

Maguire, R. P., Broerse, A., de Jong, B. M., Cornelissen, F. W., Meiners, L. C., Leenders, K. L., et al. (2003). Evidence of enhancement of spatial attention during inhibition of a visuo-motor response. *Neuroimage, 20*(2), 1339-1345.

Malenka, R. C., & Bear, M. F. (2004). LTP and LTD: an embarrassment of riches. *Neuron, 44*(1), 5-21.

Mani, T. M., Bedwell, J. S., & Miller, L. S. (2005). Age-related decrements in performance on a brief continuous performance test. *Arch Clin Neuropsychol, 20*(5), 575-586.

Mapstone, M., Rosler, A., Hays, A., Gitelman, D. R., & Weintraub, S. (2001). Dynamic allocation of attention in aging and Alzheimer disease: uncoupling of the eye and mind. *Arch Neurol, 58*(9), 1443-1447.

Maquet, P. (2000). Functional neuroimaging of normal human sleep by positron emission tomography. *J Sleep Res, 9*(3), 207-231.

Maquet, P. (2001). The role of sleep in learning and memory. *Science, 294*(5544), 1048-1052.

Maquet, P., Degueldre, C., Delfiore, G., Aerts, J., Peters, J. M., Luxen, A., et al. (1997). Functional neuroanatomy of human slow wave sleep. *J Neurosci, 17*(8), 2807-2812.

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., et al. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nat Neurosci, 3*(8), 831-836.

Maquet, P., Peters, J., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., et al. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature, 383*(6596), 163-166.

Margoliash, D. (1983). Acoustic parameters underlying the responses of song-specific neurons in the white-crowned sparrow. *J Neurosci, 3*(5), 1039-1057.

Margoliash, D. (2001). Do sleeping birds sing? Population coding and learning in the bird song system. *Prog Brain Res, 130*, 319-331.

Margoliash, D. (2005). Song learning and sleep. *Nat Neurosci, 8*(5), 546-548.

Margoliash, D., & Konishi, M. (1985). Auditory representation of autogenous song in the song system of white-crowned sparrows. *Proc Natl Acad Sci U S A, 82*(17), 5997-6000.

Marshall, L., Helgadottir, H., Molle, M., & Born, J. (2006). Boosting slow oscillations during sleep potentiates memory. *Nature, 444*(7119), 610-613.

Marshall, L., Molle, M., Hallschmid, M., & Born, J. (2004). Transcranial direct current stimulation during sleep improves declarative memory. *J Neurosci, 24*(44), 9985-9992.

Mason, T., 2nd, & Pack, A. I. (2007). Pediatric Parasomnias. *Sleep, 30*(2), 141-151.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science, 309*(5744), 2228-2232.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *J Neurosci, 24*(31), 6862-6870.

Matthews, S. C., Simmons, A. N., Arce, E., & Paulus, M. P. (2005). Dissociation of inhibition from error processing using a parametric inhibitory task during functional magnetic resonance imaging. *Neuroreport, 16*(7), 755-760.

McCarthy, M. E., & Waters, W. F. (1997). Decreased attentional responsivity during sleep deprivation: orienting response latency, amplitude, and habituation. *Sleep, 20*(2), 115-123.

McCartt, A. T., Ribner, S. A., Pack, A. I., & Hammer, M. C. (1996). The scope and nature of the drowsy driving problem in New York State. *Accid Anal Prev, 28*(4), 511-517.

McCurry, S. M., & Ancoli-Israel, S. (2003). Sleep Dysfunction in Alzheimer's Disease and Other Dementias. *Curr Treat Options Neurol, 5*(3), 261-272.

McDowd, J. M., & Filion, D. L. (1992). Aging, selective attention, and inhibitory processes: a psychophysiological approach. *Psychol Aging, 7*(1), 65-71.

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism, 55*(10 Suppl 2), S20-23.

Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: a nap is as good as a night. *Nat Neurosci, 6*(7), 697-698.

Mednick, S. C., Nakayama, K., Cantero, J. L., Atienza, M., Levin, A. A., Pathak, N., et al. (2002). The restorative effect of naps on perceptual deterioration. *Nat Neurosci, 5*(7), 677-681.

Meney, I., Waterhouse, J., Atkinson, G., Reilly, T., & Davenne, D. (1998). The effect of one night's sleep deprivation on temperature, mood, and physical performance in subjects with different amounts of habitual physical activity. *Chronobiol Int, 15*(4), 349-363.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp, 12*(3), 131-143.

Mesulam, M. M. (1981). A cortical network for directed attention and unilateral neglect. *Ann Neurol, 10*(4), 309-325.

Mesulam, M. M. (1986). Frontal cortex and behavior. *Ann Neurol, 19*(4), 320-325.

Mesulam, M. M. (1998). From sensation to cognition. *Brain, 121 (Pt 6)*, 1013-1052.

Mesulam, M. M., Nobre, A. C., Kim, Y. H., Parrish, T. B., & Gitelman, D. R. (2001). Heterogeneity of cingulate contributions to spatial attention. *Neuroimage, 13*(6 Pt 1), 1065-1072.

Mirmiran, M., van den Dungen, H., & Uylings, H. B. (1982). Sleep patterns during rearing under different environmental conditions in juvenile rats. *Brain Res, 233*(2), 287-298.

Mitler, M. M., Carskadon, M. A., Czeisler, C. A., Dement, W. C., Dinges, D. F., & Graeber, R. C. (1988). Catastrophes, sleep, and public policy: consensus report. *Sleep, 11*(1), 100-109.

Mittag, M. (1996). Conserved circadian elements in phylogenetically diverse algae. *Proc Natl Acad Sci U S A, 93*(25), 14401-14404.

Monin, A. S. (1992). On the definition of the concepts thinking, consciousness, and conscience. *Proc Natl Acad Sci U S A, 89*(13), 5774-5778.

Monjan, A. A. (1990). Sleep disorders of older people: report of a consensus conference. *Hosp Community Psychiatry, 41*(7), 743-744.

Monk, T. H., Buysse, D. J., Reynolds, C. F., 3rd, Jarrett, D. B., & Kupfer, D. J. (1992). Rhythmic vs homeostatic influences on mood, activation, and performance in young and old men. *J Gerontol, 47*(4), P221-227.

Morcom, A. M., & Fletcher, P. C. (2007). Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage, 37*(4), 1073-1082.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., et al. (1989). The consortium to establish a registry for Alzheimer's disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology, 39*(9), 115-1165.

Moruzzi, G., & Mangoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Clin Neurophysiol, 1*, 455-473.

Mu, Q., Mishory, A., Johnson, K. A., Nahas, Z., Kozel, F. A., Yamanaka, K., et al. (2005). Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. *Sleep, 28*(4), 433-446.

Murphy, K., & Garavan, H. (2005). Deriving the optimal number of events for an event-related fMRI study based on the spatial extent of activation. *Neuroimage, 27*(4), 771-777.

National Sleep Foundation. (2005). *Sleep in America Poll*. Washington, D.C.: National Sleep Foundation.

Naylor, E., Bergmann, B. M., Krauski, K., Zee, P. C., Takahashi, J. S., Vitaterna, M. H., et al. (2000). The circadian clock mutation alters sleep homeostasis in the mouse. *J Neurosci, 20*(21), 8138-8143.

Nessler, D., Friedman, D., Johnson, R., Jr., & Bersick, M. (2006). ERPs suggest that age affects cognitive control but not response conflict detection. *Neurobiol Aging*.

Netzer, N. C., Stoohs, R. A., Netzer, C. M., Clark, K., & Strohl, K. P. (1999). Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med, 131*(7), 485-491.

Nielsen, T. A. (2000). A review of mentation in REM and NREM sleep: "covert" REM sleep as a possible reconciliation of two opposing models. *Behav Brain Sci, 23*(6), 851-866; discussion 904-1121.

Nielson, K. A., Langenecker, S. A., & Garavan, H. (2002). Differences in the functional neuroanatomy of inhibitory control across the adult life span. *Psychol Aging, 17*(1), 56-71.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. *Psychol Bull, 126*(2), 220-246.

Nilsson, L. G., Backman, L., & Karlsson, T. (1989). Priming and cued recall in elderly, alcohol intoxicated and sleep deprived subjects: a case of functionally similar memory deficits. *Psychol Med, 19*(2), 423-433.

Nobre, A. C., Gitelman, D. R., Dias, E. C., & Mesulam, M. (2000). Covert Visual Spatial Orienting and Saccades: Overlapping Neural Systems. *Neuroimage, 11*, 210-216.

Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain, 120 (Pt 3)*, 515-533.

Nofzinger, E. A., Buysse, D. J., Germain, A., Price, J. C., Miewald, J. M., & Kupfer, D. J. (2004). Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry, 161*(11), 2126-2128.

Nofzinger, E. A., Buysse, D. J., Miewald, J. M., Meltzer, C. C., Price, J. C., Sembrat, R. C., et al. (2002). Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain, 125*(Pt 5), 1105-1115.

Nofzinger, E. A., Mintun, M. A., Wiseman, M., Kupfer, D. J., & Moore, R. Y. (1997). Forebrain activation in REM sleep: an FDG PET study. *Brain Res, 770*(1-2), 192-201.

Nordeen, K. W., & Nordeen, E. J. (1992). Auditory feedback is necessary for the maintenance of stereotyped song in adult zebra finches. *Behav Neural Biol, 57*(1), 58-66.

Norton, R. (1970). The effects of acute sleep deprivation on selective attention. *Br J Psychol, 61*(2), 157-161.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci, 14*(8), 1215-1229.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872.

Oken, B. S., Salinsky, M. C., & Elsas, S. M. (2006). Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clin Neurophysiol, 117*(9), 1885-1901.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Pack, A. I., Pack, A. M., Rodgman, E., Cucchiara, A., Dinges, D. F., & Schwab, C. W. (1995). Characteristics of crashes attributed to the driver having fallen asleep. *Accid Anal Prev, 27*(6), 769-775.

Paller, K. A., & Voss, J. L. (2004). Memory reactivation and consolidation during sleep. *Learn Mem, 11*(6), 664-670.

Parasuraman, R., & Giambra, L. (1991). Skill development in vigilance: effects of event rate and age. *Psychol Aging, 6*(2), 155-169.

Parasuraman, R., Nestor, P., & Greenwood, P. (1989). Sustained-attention capacity in young and older adults. *Psychol Aging, 4*(3), 339-345.

Patrick, G. T. W., & Gilbert, J. A. (1896). On the effects of loss of sleep. *The psychological review, 3*(5), 468-483.

Perchet, C., Revol, O., Fourneret, P., Mauguiere, F., & Garcia-Larrea, L. (2001). Attention shifts and anticipatory mechanisms in hyperactive children: an ERP study using the Posner paradigm. *Biol Psychiatry, 50*(1), 44-57.

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: a link to cognitive control? *J Cogn Neurosci, 19*(6), 1021-1032.

Philip, P., Taillard, J., Sagaspe, P., Valtat, C., Sanchez-Ortuno, M., Moore, N., et al. (2004). Age, performance and sleep deprivation. *J Sleep Res, 13*(2), 105-110.

Pieron, H. (1913). *Le probleme physiologique du Sommeil*. Paris, Masson et Cie.

Pilcher, J. J., & Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep, 19*(4), 318-326.

Pittendrigh, C. S., & Daan, S. (1974). Circadian oscillations in rodents: a systematic increase of their frequency with age. *Science, 186*(4163), 548-550.

Plautz, J. D., Kaneko, M., Hall, J. C., & Kay, S. A. (1997). Independent photoreceptive circadian clocks throughout Drosophila. *Science, 278*(5343), 1632-1635.

Plihal, W., & Born, J. (1999a). Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology, 36*(5), 571-582.

Plihal, W., & Born, J. (1999b). Memory consolidation in human sleep depends on inhibition of glucocorticoid release. *Neuroreport, 10*(13), 2741-2747.

Plihal, W., Pietrowsky, R., & Born, J. (1999). Dexamethasone blocks sleep induced improvement of declarative memory. *Psychoneuroendocrinology, 24*(3), 313-331.

Polzella, D. J. (1975). Effects of sleep deprivation on short-term recognition memory. *J Exp Psychol [Hum Learn], 104*(2), 194-200.

Porkka-Heiskanen, T., Alanko, L., Kalinchuk, A., & Stenberg, D. (2002). Adenosine and sleep. *Sleep Med Rev, 6*(4), 321-332.

Porkka-Heiskanen, T., Strecker, R. E., Thakkar, M., Bjorkum, A. A., Greene, R. W., & McCarley, R. W. (1997). Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science, 276*(5316), 1265-1268.

Portas, C. M., Rees, G., Howseman, A. M., Josephs, O., Turner, R., & Frith, C. D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *J Neurosci, 18*(21), 8979-8989.

Posner, M. I. (1980). Orienting of attention. *Q J Exp Psychol, 32*(1), 3-25.

Posner, M. I. (1994). Attention: the mechanisms of consciousness. *Proc Natl Acad Sci U S A, 91*(16), 7398-7403.

Posner, M. I., Inhoff, A. W., & Friedrich, F. J. (1987). Isolating attentional systems: A cognitive-anatomical analysis. *Psychobiology, 15*(2), 107-121.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annu Rev Neurosci, 13*, 25-42.

Quintilian. (1922). Institutio Oratoria. In H. E. Butler (Ed.), *Training of an Orator* (Vol. IV (Book XI, Chapter 2), pp. 237-239): Loeb Classical Library.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37*(4), 1083-1090; discussion 1097-1089.

Raidy, D. J., & Scharff, L. F. (2005). Effects of sleep deprivation on auditory and visual memory tasks. *Percept Mot Skills, 101*(2), 451-467.

Ralph, M. R., Foster, R. G., Davis, F. C., & Menaker, M. (1990). Transplanted suprachiasmatic nucleus determines circadian period. *Science, 247*(4945), 975-978.

Ralph, M. R., & Menaker, M. (1988). A mutation of the circadian system in golden hamsters. *Science, 241*(4870), 1225-1227.

Rasch, B., Buchel, C., Gais, S., & Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science, 315*(5817), 1426-1429.

Rauske, P. L., Shea, S. D., & Margoliash, D. (2003). State and neuronal class-dependent reconfiguration in the avian song system. *J Neurophysiol, 89*(3), 1688-1701.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb Cortex, 7*(3), 268-282.

Rechtschaffen, A., Gilliland, M. A., Bergmann, B. M., & Winter, J. B. (1983). Physiological correlates of prolonged sleep deprivation in rats. *Science, 221*(4606), 182-184.

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques an scoring system of sleep stages in human subjects.* Los Angeles: UCLA Brain Information Services.

Rediehs, M. H., Reis, J. S., & Creason, N. S. (1990). Sleep in old age: focus on gender differences. *Sleep, 13*(5), 410-424.

Reid, K., & Dawson, D. (2001). Comparing performance on a simulated 12 hour shift rotation in young and older subjects. *Occup Environ Med, 58*(1), 58-62.

Reid, K. J., Chang, A. M., Dubocovich, M. L., Turek, F. W., Takahashi, J. S., & Zee, P. C. (2001). Familial advanced sleep phase syndrome. *Arch Neurol, 58*(7), 1089-1094.

Reitan, R. M. (1958). Validity of the trail-making test as an indication of organic brain damage. *Percept Mot Skills, 8*, 271-276.

Resnick, S. M., Pham, D. L., Kraut, M. A., Zonderman, A. B., & Davatzikos, C. (2003). Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J Neurosci, 23*(8), 3295-3301.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., et al. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J Cogn Neurosci, 12*(1), 174-187.

Reyner, L. A., & Horne, J. A. (1997). Suppression of sleepiness in drivers: combination of caffeine with a short nap. *Psychophysiology, 34*(6), 721-725.

Reyner, L. A., & Horne, J. A. (1998). Evaluation "in-car" countermeasures to sleepiness: cold air and radio. *Sleep, 21*(1), 46-50.

Reynolds, C. F., 3rd, Kupfer, D. J., Hoch, C. C., Stack, J. A., Houck, P. R., & Berman, S. R. (1986). Sleep deprivation in healthy elderly men and women: effects on mood and on sleep during recovery. *Sleep, 9*(4), 492-501.

Ribeiro, S., Goyal, V., Mello, C. V., & Pavlides, C. (1999). Brain gene expression during REM sleep depends on prior waking experience. *Learn Mem, 6*(5), 500-508.

Ribeiro, S., Mello, C. V., Velho, T., Gardner, T. J., Jarvis, E. D., & Pavlides, C. (2002). Induction of hippocampal long-term potentiation during waking leads to increased extrahippocampal zif-268 expression during ensuing rapid-eye-movement sleep. *J Neurosci, 22*(24), 10914-10923.

Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: an fMRI study. *Neuropsychologia, 38*(3), 325-335.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443-447.

Robinson, D. L., Bowman, E. M., & Kertzman, C. (1995). Covert orienting of attention in macaques. II. Contributions of parietal cortex. *J Neurophysiol, 74*(2), 698-712.

Rosa, R. R., Bonnet, M. H., & Warm, J. S. (1983). Recovery of performance during sleep following sleep deprivation. *Psychophysiology, 20*(2), 152-159.

Rowe, J. B., Toni, I., Josephs, O., Frackowiak, R. S., & Passingham, R. E. (2000). The prefrontal cortex: response selection or maintenance within working memory? *Science, 288*(5471), 1656-1660.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., et al. (2001). Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage, 13*(2), 250-261.

Rubia, K., Smith, A. B., Brammer, M. J., & Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage, 20*(1), 351-358.

Ruff, C. C., Woodward, T. S., Laurens, K. R., & Liddle, P. F. (2001). The role of the anterior cingulate cortex in conflict processing: evidence from reverse stroop interference. *Neuroimage, 14*(5), 1150-1158.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nat Neurosci, 3*(5), 509-515.

Sagaspe, P., Sanchez-Ortuno, M., Charles, A., Taillard, J., Valtat, C., Bioulac, B., et al. (2006). Effects of sleep deprivation on Color-Word, Emotional, and Specific Stroop interference and on self-reported anxiety. *Brain Cogn, 60*(1), 76-87.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol Rev, 103*(3), 403-428.

Salvador, R., Suckling, J., Coleman, M. R., Pickard, J. D., Menon, D., & Bullmore, E. (2005). Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex, 15*(9), 1332-1342.

Saper, C. B., Chou, T. C., & Scammell, T. E. (2001). The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci, 24*(12), 726-731.

Schacter, D. L., Savage, C. R., Alpert, N. M., Rauch, S. L., & Albert, M. S. (1996). The role of hippocampus and frontal cortex in age-related memory changes: a PET study. *Neuroreport, 7*(6), 1165-1169.

Scheffers, M. K., Humphrey, D. G., Stanny, R. R., Kramer, A. F., & Coles, M. G. (1999). Error-related processing during a period of extended wakefulness. *Psychophysiology, 36*(2), 149-157.

Scheibel, M. E., & Scheibel, A. B. (1966). The organization of the nucleus reticularis thalami: A golgi study. *Brain Res, 1*, 43-62.

Schibler, U., & Sassone-Corsi, P. (2002). A web of circadian pacemakers. *Cell, 111*(7), 919-922.

Schulze, G. (2004). Sleep protects excitatory cortical circuits against oxidative damage. *Med Hypotheses, 63*(2), 203-207.

Schwartz, S., Maquet, P., & Frith, C. (2002). Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination. *Proc Natl Acad Sci U S A, 99*(26), 17137-17142.

Shaw, P. J., Tononi, G., Greenspan, R. J., & Robinson, D. F. (2002). Stress response genes protect against lethal effects of sleep deprivation in Drosophila. *Nature, 417*(6886), 287-291.

Shea, S. D., & Margoliash, D. (2003). Basal forebrain cholinergic modulation of auditory activity in the zebra finch song system. *Neuron, 40*(6), 1213-1226.

Siapas, A. G., & Wilson, M. A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron, 21*(5), 1123-1128.

Siegel, J. M. (1995). Phylogeny and the function of REM sleep. *Behav Brain Res, 69*(1-2), 29-34.

Siegel, J. M. (2001). The REM sleep-memory consolidation hypothesis. *Science, 294*(5544), 1058-1063.

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia, 46*(1), 224-232.

Small, D. M., Gitelman, D. R., Gregory, M. D., Nobre, A. C., Parrish, T. B., & Mesulam, M. M. (2003). The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. *Neuroimage, 18*(3), 633-641.

Small, D. M., Voss, J., Mak, Y. E., Simmons, K. B., Parrish, T., & Gitelman, D. (2004). Experience-dependent neural integration of taste and smell in the human brain. *J Neurophysiol, 92*(3), 1892-1903.

Smith, C. (1985). Sleep states and learning: a review of the animal literature. *Neurosci Biobehav Rev, 9*(2), 157-168.

Smith, C., Young, J., & Young, W. (1980). Prolonged increases in paradoxical sleep during and after avoidance-task acquisition. *Sleep, 3*(1), 67-81.

Smith, G. S., Reynolds, C. F., 3rd, Pollock, B., Derbyshire, S., Nofzinger, E., Dew, M. A., et al. (1999). Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. *Am J Psychiatry, 156*(5), 683-689.

Snyder, S. H., Katims, J. J., Annau, Z., Bruns, R. F., & Daly, J. W. (1981). Adenosine receptors and behavioral actions of methylxanthines. *Proc Natl Acad Sci U S A, 78*(5), 3260-3264.

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nat Neurosci, 6*(3), 309-315.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet, 354*(9188), 1435-1439.

Spiegel, K., Sheridan, J. F., & Van Cauter, E. (2002). Effect of sleep deprivation on response to immunization. *Jama, 288*(12), 1471-1472.

Stephan, F. K., & Zucker, I. (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc Natl Acad Sci U S A, 69*(6), 1583-1586.

Steriade, M., Deschenes, M., Domich, L., & Mulle, C. (1985). Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol, 54*(6), 1473-1497.

Steriade, M., Domich, L., & Oakson, G. (1986). Reticularis thalami neurons revisited: activity changes during shifts in states of vigilance. *J Neurosci, 6*(1), 68-81.

Steriade, M., Domich, L., Oakson, G., & Deschenes, M. (1987). The deafferented reticular thalamic nucleus generates spindle rhythmicity. *J Neurophysiol, 57*(1), 260-273.

Stickgold, R. (2001). Toward a cognitive neuroscience of sleep. *Sleep Med Rev, 5*(6), 417-421.

Stickgold, R. (2005). Sleep-dependent memory consolidation. *Nature, 437*(7063), 1272-1278.

Stickgold, R., Fosse, R., & Walker, M. P. (2002). Linking brain and behavior in sleep-dependent learning and memory consolidation. *Proc Natl Acad Sci U S A, 99*(26), 16519-16521.

Stickgold, R., Hobson, J. A., Fosse, R., & Fosse, M. (2001). Sleep, learning, and dreams: off-line memory reprocessing. *Science, 294*(5544), 1052-1057.

Stickgold, R., James, L., & Hobson, J. A. (2000). Visual discrimination learning requires sleep after training. *Nat Neurosci, 3*(12), 1237-1238.

Stickgold, R., Malia, A., Maguire, D., Roddenberry, D., & O'Connor, M. (2000). Replaying the game: hypnagogic images in normals and amnesics. *Science, 290*(5490), 350-353.

Stickgold, R., Scott, L., Rittenhouse, C., & Hobson, J. A. (1999). Sleep-induced changes in associative memory. *J Cogn Neurosci, 11*(2), 182-193.

Stickgold, R., & Walker, M. P. (2005a). Memory consolidation and reconsolidation: what is the role of sleep? *Trends Neurosci, 28*(8), 408-415.

Stickgold, R., & Walker, M. P. (2005b). Sleep and memory: the ongoing debate. *Sleep, 28*(10), 1225-1227.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., & Hobson, J. A. (2000). Visual discrimination task improvement: A multi-step process occurring during sleep. *J Cogn Neurosci, 12*(2), 246-254.

Strangman, G., Thompson, J. H., Strauss, M. M., Marshburn, T. H., & Sutton, J. P. (2005). Functional brain imaging of a complex navigation task following one night of total sleep deprivation: a preliminary study. *J Sleep Res, 14*(4), 369-375.

Swaab, D. F., Fliers, E., & Partiman, T. S. (1985). The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. *Brain Res, 342*(1), 37-44.

Tagney, J. (1973). Sleep patterns related to rearing rats in enriched and impoverished environments. *Brain Res, 53*(2), 353-361.

Tailairach, J., & Tournoux, P. (1988). *Steriotaxic Atlas of the human brain*. New York: Thieme Medical.

Thomas, M., Sing, H., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res, 9*(4), 335-352.

Thompson, J. K., Peterson, M. R., & Freeman, R. D. (2003). Single-neuron activity and tissue oxygenation in the cerebral cortex. *Science, 299*(5609), 1070-1072.

Thompson, K. G., Biscoe, K. L., & Sato, T. R. (2005). Neuronal basis of covert spatial attention in the frontal eye field. *J Neurosci, 25*(41), 9479-9487.

Thorne, D. R., Johnson, D. E., Redmond, D. P., Sing, H. C., Belenky, G., & Shapiro, J. M. (2005). The Walter Reed palm-held psychomotor vigilance test. *Behav Res Methods, 37*(1), 111-118.

Toh, K. L., Jones, C. R., He, Y., Eide, E. J., Hinz, W. A., Virshup, D. M., et al. (2001). An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science, 291*(5506), 1040-1043.

Tononi, G., & Cirelli, C. (2003). Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull, 62*(2), 143-150.

Tononi, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Med Rev, 10*(1), 49-62.

Tononi, G., & Koch, C. (2008). The neural correlates of consciousness: an update. *Ann N Y Acad Sci, 1124*, 239-261.

Toth, M., Kiss, A., Kosztolanyi, P., & Kondakor, I. (2007). Diurnal alterations of brain electrical activity in healthy adults: a LORETA study. *Brain Topogr, 20*(2), 63-76.

Townsend, J., Adamo, M., & Haist, F. (2006). Changing channels: an fMRI study of aging and cross-modal attention shifts. *Neuroimage, 31*(4), 1682-1692.

Trachtenberg, J. T., Chen, B. E., Knott, G. W., Feng, G., Sanes, J. R., Welker, E., et al. (2002). Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature, 420*(6917), 788-794.

Tsai, L. L., Young, H. Y., Hsieh, S., & Lee, C. S. (2005). Impairment of error monitoring following sleep deprivation. *Sleep, 28*(6), 707-713.

Tulving, E., Kapur, S., Craik, F. I., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A, 91*(6), 2016-2020.

Turek, F. W. (1998). Circadian rhythms. *Horm Res, 49*(3-4), 109-113.

Turek, F. W., Dugovic, C., & Zee, P. C. (2001). Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch Neurol, 58*(11), 1781-1787.

Turner, T. H., Drummond, S. P., Salamat, J. S., & Brown, G. G. (2007). Effects of 42 hr of total sleep deprivation on component processes of verbal working memory. *Neuropsychology, 21*(6), 787-795.

Ursu, S., Stenger, V. A., Shear, M. K., Jones, M. R., & Carter, C. S. (2003). Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci, 14*(4), 347-353.

Van Cauter, E. (1990). Diurnal and ultradian rhythms in human endocrine function: a minireview. *Horm Res, 34*(2), 45-53.

Van Cauter, E., Leproult, R., & Plat, L. (2000). Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. *Jama, 284*(7), 861-868.

Van Dongen, H. P., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep, 27*(3), 423-433.

Van Dongen, H. P., Caldwell, J. A., Jr., & Caldwell, J. L. (2006). Investigating systematic individual differences in sleep-deprived performance on a high-fidelity flight simulator. *Behav Res Methods, 38*(2), 333-343.

Van Dongen, H. P., Maislin, G., Mullington, J. M., & Dinges, D. F. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep, 26*(2), 117-126.

Van Dongen, H. P., Mott, C. G., Huang, J. K., Mollicone, D. J., McKenzie, F. D., & Dinges, D. F. (2007). Optimization of biomathematical model predictions for cognitive performance impairment in individuals: accounting for unknown traits and uncertain states in homeostatic and circadian processes. *Sleep, 30*(9), 1129-1143.

Venkatraman, V., Chuah, Y. M., Huettel, S. A., & Chee, M. W. (2007). Sleep deprivation elevates expectation of gains and attenuates response to losses following risky decisions. *Sleep, 30*(5), 603-609.

Vertes, R. P., & Siegel, J. M. (2005). Time for the sleep community to take a critical look at the purported role of sleep in memory processing. *Sleep, 28*(10), 1228-1229; discussion 1230-1223.

Vogt, B. A., & Laureys, S. (2005). Posterior cingulate, precuneal and retrosplenial cortices: cytology and components of the neural network correlates of consciousness. *Prog Brain Res, 150*, 205-217.

von Economo, C. (1930). Sleep as a problem of localization. *J Nerv Ment Dis, 71*(3), 249-259.

Vyazovskiy, V. V., Cirelli, C., Pfister-Genskow, M., Faraguna, U., & Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci, 11*(2), 200-208.

Wager, T. D., Jonides, J., & Smith, E. E. (2006). Individual differences in multiple types of shifting attention. *Mem Cognit, 34*(8), 1730-1743.

Wagner, U., Gais, S., & Born, J. (2001). Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learn Mem, 8*(2), 112-119.

Wagner, U., Gais, S., Haider, H., Verleger, R., & Born, J. (2004). Sleep inspires insight. *Nature, 427*(6972), 352-355.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron, 35*(1), 205-211.

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A., & Stickgold, R. (2003). Sleep and the time course of motor skill learning. *Learn Mem, 10*(4), 275-284.

Walker, M. P., & Stickgold, R. (2004). Sleep-dependent learning and memory consolidation. *Neuron, 44*(1), 121-133.

Walker, M. P., & Stickgold, R. (2006). Sleep, memory, and plasticity. *Annu Rev Psychol, 57*, 139-166.

Walker, M. P., Stickgold, R., Alsop, D., Gaab, N., & Schlaug, G. (2005). Sleep-dependent motor memory plasticity in the human brain. *Neuroscience, 133*(4), 911-917.

Walker, M. P., Stickgold, R., Jolesz, F. A., & Yoo, S. S. (2005). The functional anatomy of sleep-dependent visual skill learning. *Cereb Cortex, 15*(11), 1666-1675.

Warren, N., & Clark, B. (1937). Blocking in mental and motor tasks during a 65-hour vigil. *Journal of Experimental Psychology, 21*, 97-105.

Watanabe, J., Sugiura, M., Sato, K., Sato, Y., Maeda, Y., Matsue, Y., et al. (2002). The human prefrontal and parietal association cortices are involved in NO-GO performances: an event-related fMRI study. *Neuroimage, 17*(3), 1207-1216.

Webb, W. B. (1981). Sleep stage responses of older and younger subjects after sleep deprivation. *Electroencephalogr Clin Neurophysiol, 52*(4), 368-371.

Webb, W. B. (1985). A further analysis of age and sleep deprivation effects. *Psychophysiology, 22*(2), 156-161.

Webb, W. B., & Agnew, H. W., Jr. (1965). Sleep: effects of a restricted regime. *Science, 150*(704), 1745-1747.

Webb, W. B., & Agnew, H. W., Jr. (1974). The effects of a chronic limitation of sleep length. *Psychophysiology, 11*(3), 265-274.

Webb, W. B., & Agnew, H. W., Jr. (1977). Analysis of the sleep stages in sleep-wakefulness regimens of varied length. *Psychophysiology, 14*(5), 445-450.

Webb, W. B., & Campbell, S. S. (1979). The first night effect revisited with age as a variable. *Waking Sleeping, 3*(4), 319-324.

Webb, W. B., & Campbell, S. S. (1980). Awakenings and the return to sleep in an older population. *Sleep, 3*(1), 41-46.

Webb, W. B., & Levy, C. M. (1982). Age, sleep deprivation, and performance. *Psychophysiology, 19*(3), 272-276.

Webb, W. B., & Levy, C. M. (1984). Effects of spaced and repeated total sleep deprivation. *Ergonomics, 27*(1), 45-58.

Wechsler, D. (1987). *Wechsler Memory Scale-Revised Manual.* San Antonio, Texas: The Psychological Corporation.

Weitzman, E. D., Moline, M. L., Czeisler, C. A., & Zimmerman, J. C. (1982). Chronobiology of aging: temperature, sleep-wake rhythms and entrainment. *Neurobiol Aging, 3*(4), 299-309.

Wenderoth, N., Debaere, F., Sunaert, S., & Swinnen, S. P. (2005). The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour. *Eur J Neurosci, 22*(1), 235-246.

West, R., & Schwarb, H. (2006). The influence of aging and frontal function on the neural correlates of regulative and evaluative aspects of cognitive control. *Neuropsychology, 20*(4), 468-481.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull, 120*(2), 272-292.

Weyerer, S., & Dilling, H. (1991). Prevalence and treatment of insomnia in the community: results from the Upper Bavarian Field Study. *Sleep, 14*(5), 392-398.

Wilkins, R. H., & Brody, I. A. (1968). Neurological classics IV. Encephalitis lethargica. *Arch Neurol, 18*(3), 324-328.

Wilkinson, R. T. (1961). Interaction of lack of sleep with knowledge of results, repeated testing, and individual differences. *J Exp Psychol, 62*, 263-271.

Wilkinson, R. T. (1969). Sleep deprivation: Performance tests for partial and selective sleep deprivation. In L. E. Abt & B. F. Riess (Eds.), *Progress in clinical psychology* (Vol. 8, pp. 28-43). New York: Grune and Stratton.

Williams, H. L., Gieseking, C. F., & Lubin, A. (1966). Some effects of sleep loss on memory. *Percept Mot Skills, 23*(3), 1287-1293.

Williams, H. L., Lubin, A., & Goodnow, J. J. (1959). Impaired performance with acute sleep loss. *Psychol Monogr, 73*(14), 484.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. *Science, 265*(5172), 676-679.

Wisor, J. P., O'Hara, B. F., Terao, A., Selby, C. P., Kilduff, T. S., Sancar, A., et al. (2002). A role for cryptochromes in sleep regulation. *BMC Neurosci, 3*, 20.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4*, 58-73.

Wright, K. P., Jr., Hull, J. T., & Czeisler, C. A. (2002). Relationship between alertness, performance, and body temperature in humans. *Am J Physiol Regul Integr Comp Physiol, 283*(6), R1370-1377.

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Chen, P., Keator, D. B., Khosla Wu, N., et al. (2006). Frontal lobe metabolic decreases with sleep deprivation not totally reversed by recovery sleep. *Neuropsychopharmacology, 31*(12), 2783-2792.

Wu, J. C., Gillin, J. C., Buchsbaum, M. S., Hershey, T., Hazlett, E., Sicotte, N., et al. (1991). The effect of sleep deprivation on cerebral glucose metabolic rate in normal humans assessed with positron emission tomography. *Sleep, 14*(2), 155-162.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res, 17*(1), 37-49.

Yoo, S. S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain without sleep--a prefrontal amygdala disconnect. *Curr Biol, 17*(20), R877-878.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., & Badr, S. (1993). The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med, 328*(17), 1230-1235.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med, 165*(9), 1217-1239.

Zhdanova, I. V. (2006). Sleep in zebrafish. *Zebrafish, 3*(2), 215-226.

Vita

Bryce Anthony Mander

Biographical Information

Born April 13, 1978 in High Point, North Carolina, USA.

Education and Training

9/2002-12/2008: Northwestern University Interdepartmental Neuroscience Ph.D Program.

9/1996-6/2000: University of Chicago: BA in Psychology.

Research Experience

4/2003-12/2008: Biological Rhythms and Sleep Research Laboratory, graduate student under Dr. Phyllis Zee, Northwestern Memorial Hospital, Department of Neurology.

6/1999-9/2002: Laboratory of Sleep, Chronobiology, and Neuroendocrinology, Research Recruiter, under Dr. Eve Van Cauter, University of Chicago, Department of Medicine, Section of Endocrinology.

Scientific Societies

Sleep Research Society

Organization for Human Brain Mapping

Publications

Ryden, A.M., Knutson, K.L., Mander, B.A., Van Cauter, E.Y. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Arch Intern Med* 2006 166(16):1768-74.

Mander, B.A., Reid, K., Davuluri, V., Small D.M., Parrish T.B., Mesulam, M.-M., Zee, P.Z., Gitelman, D.R. Sleep loss alters functioning within the neural network underlying the covert orienting of attention. *Brain Res* 2008, 1217:148-56.

Research Support

NIH/NIMH, 1F31 MH074291 "The neural response to sleep loss in the elderly" (PI: Mander)

Project Period: 9/05-8/08. *The objectives of this grant are to determine the effects of sleep loss on endogenous visual spatial attention and inhibitory control in the young and elderly using functional imaging.*