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Predictors Of Interindividual Differences In Vulnerability To Neurobehavioral Consequences Of Chronic Partial Sleep Restriction

Abstract

Interindividual differences in neurobehavioral response to sleep loss are ubiquitous and unexplained. Numerous factors have been examined as potential predictors of phenotypic response to sleep loss but none have yielded a comprehensive view of the phenomenon. This dissertation examines the impact of baseline factors, habitual sleep patterns, and homeostatic response to sleep loss on accrued deficits in psychomotor vigilance during chronic partial sleep restriction, using the largest study sample to date. A total of 306 healthy adults completed controlled isolated laboratory protocols for 11-20 days and were randomized to either chronic partial sleep restriction (five consecutive nights of four hours time in bed) or control condition (ten hours time in bed on all nights). Findings indicate no significant impact of personality, academic intelligence, subjective reports of chronotype, sleepiness and fatigue, performance on working memory, and demographic factors such as sex, ethnicity, and body mass index, on vulnerability to the negative effects of sleep loss on psychomotor vigilance. Superior baseline performance on the PVT, older age, and ability to sustain wakefulness on the MWT were associated with relative resilience to decrements in vigilant attention during sleep restriction. Interindividual differences in vulnerability to the effects of sleep loss were not accounted for by prior sleep history, habitual sleep patterns outside of the laboratory, baseline sleep architecture, or homeostatic sleep response during chronic partial sleep restriction. Variability in a modulatory drive responsible for integrating competing signals for wakefulness and sleep may partially account for phenotypic vulnerability to the effects of sleep loss.

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PREDICTORS OF INTERINDIVIDUAL DIFFERENCES IN VULNERABILITY TO
NEUROBEHAVIORAL CONSEQUENCES OF CHRONIC PARTIAL SLEEP RESTRICTION

Olga Galli

A DISSERTATION

in

Psychology

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2020

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PREDICTORS OF INTERINDIVIDUAL DIFFERENCES IN VULNERABILITY TO
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ABSTRACT

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Olga Galli

Dr. David F. Dinges

Interindividual differences in neurobehavioral response to sleep loss are ubiquitous and unexplained. Numerous factors have been examined as potential predictors of phenotypic response to sleep loss but none have yielded a comprehensive view of the phenomenon. This dissertation examines the impact of baseline factors, habitual sleep patterns, and homeostatic response to sleep loss on accrued deficits in psychomotor vigilance during chronic partial sleep restriction, using the largest study sample to date. A total of 306 healthy adults completed controlled isolated laboratory protocols for 11-20 days and were randomized to either chronic partial sleep restriction (five consecutive nights of four hours time in bed) or control condition (ten hours time in bed on all nights). Findings indicate no significant impact of personality, academic intelligence, subjective reports of chronotype, sleepiness and fatigue, performance on working memory, and demographic factors such as sex, ethnicity, and body mass index, on vulnerability to the negative effects of sleep loss on psychomotor vigilance. Superior baseline performance on the PVT, older age, and ability to sustain wakefulness on the MWT were associated with relative resilience to decrements in vigilant attention during sleep restriction. Interindividual differences in vulnerability to the effects of sleep loss were not accounted for by prior sleep history, habitual sleep patterns outside of the laboratory, baseline sleep architecture, or homeostatic sleep response during chronic partial sleep restriction. Variability in a modulatory drive responsible for integrating competing signals for wakefulness and sleep may partially account for phenotypic vulnerability to the effects of sleep loss.

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CHAPTER 1: INTRODUCTION

Sleep is ubiquitous within the animal kingdom. To date, not a single animal has been observed to survive entirely without sleep, although recent findings are beginning to cast doubt on this assumption (Geissmann, Beckwith, & Gilestro, 2019). Various functions of sleep have been proposed, including energy conservation, avoidance of predators, neuronal maintenance, learning and memory consolidation, immune functioning, and glymphatic clearance of toxic waste (Benington & Craig Heller, 1995; Berger & Phillips, 1995; Imeri & Opp, 2009; Lesku et al., 2008; Lima & Rattenborg, 2007; Majde & Krueger, 2005; Meddis, 1975; Preston, Capellini, McNamara, Barton, & Nunn, 2009; M. H. Schmidt, 2014; Stickgold & Walker, 2005; Tononi & Cirelli, 2006; Xie et al., 2013). While the debate for a single fundamental function for sleep continues, it is abundantly clear that sleep is necessary for survival and evolutionary success (Cirelli & Tononi, 2008; Allan Rechtschaffen, 1998).

How much sleep one obtains is influenced by many factors such as physical and mental health, social and professional obligations, and the availability of desirable alternatives. Modern social and economic factors such as globalization, work demands, and social pressures promote the continuous expansion of wakefulness at the expense of sleep opportunity. Individuals today are getting less sleep, which may contribute to increased fatigue during the daytime, diminished work performance, and greater probability of errors and dangerous behavior, especially while operating machinery or driving (Knutson, Van Cauter, Rathouz, DeLeire, & Lauderdale, 2010). Data from over 47,000 respondents to the American Time Use Survey found a strong negative association between sleep duration and time spent engaged in other activities, particularly compensated work time and commuting to and from work. The survey highlighted the choice individuals make on a regular basis between longer sleep and engaging in other motivated behaviors (Basner et al., 2007).

Insufficient sleep is associated with greater morbidity, mortality, and financial costs (Leger, 1994). Reports of medical incidents and performance failures have consistently cited insufficient sleep or human error as a result of sleep loss as a contributing factor. Sleep pathology, voluntary curtailment of sleep, and circadian misalignment have been linked with motor vehicle accidents (J. A. Horne & Reyner, 1995; Jim Horne & Reyner, 1999; Philip & Åkerstedt, 2006; Reinach & Viale, 2006), occupational accidents (T. Åkerstedt, Fredlund, Gillberg, & Jansson, 2002), aviation accidents (Caldwell, 2005), failures in combat operations (Giam, 1997), and medical errors (Barger et al., 2006; Kramer, 2010; Parker & Parker, 2017; Patterson et al., n.d.; Weinger & Ancoli-Israel, 2002), as well as major disasters such as the grounding of the Exxon Valdez oil tanker and nuclear plant accidents at Three Mile Island and Chernobyl (Mittler et al., 1988).

In the laboratory, sleep loss results in deficits on a wide range of cognitive and affective measures. Much of what is now known is based on studies of total sleep deprivation, which have illustrated reduced alertness, slower cognitive processing, impaired judgment, increased errors, as well as elevations in subjective ratings of psychopathology (D F Dinges & Kribbs, 1991; Goel, Rao, Durmer, & Dinges, 2009a; Harrison & Horne, 2000; William D S Killgore, Balkin, & Wesensten, 2006; Lim & Dinges, 2010; Pilcher & Huffcutt, 1996; Reynolds & Banks, 2010). More recently, the focus has shifted toward the effects of chronic partial sleep restriction, rather than acute total sleep deprivation. The standard experimental model of five nights of sleep restriction to 4-6 hours per night is a more accurate reflection of typical sleep schedules in which individuals restrict sleep during the workweek to accommodate more opportunities, and extend sleep on the weekends in an attempt to compensate for any deficits accrued over the previous week. There is evidence that chronic sleep restriction has significant effects on a wide range of cognitive, behavioral, and health measures, and that even mild to moderate sleep restriction over a prolonged period of time has profound effects on cognitive functioning, often beyond that what is seen with acute total sleep deprivation (Van Dongen, Maislin, Mullington, & Dinges, 2003). These

decrements in performance on neurobehavioral tasks, as well as increased subjective sleepiness and fatigue, tend to accumulate with each day of successive sleep restriction (Banks & Dinges, 2007; Carskadon & Dement, 1981; D F Dinges et al., 1997). It is uncertain whether extended recovery sleep opportunity over one or two days is sufficient for complete recovery from these deficits for all types of cognitive function, with evidence suggesting that different aspects of cognition may require varying amounts of sleep to return to baseline (Banks, Dongen, Maislin, & Dinges, 2010; Belenky et al., 2003; Lamond et al., 2007).

Large interindividual differences in vulnerability to the effects of sleep loss have been demonstrated in measures of neurobehavioral performance, subjective reports of sleepiness and fatigue, and physiological response. Until recently, this between-subject variance has been largely ignored or modeled as random error. However, such interpersonal differences have been shown to be stable across repeated exposures to sleep loss separated by days or even years, and across total sleep deprivation and partial chronic sleep restriction (Dennis, Wohl, Selame, & Goel, 2017).

The Psychomotor Vigilance Task (PVT) is an established measure of simple sustained attention which has been identified as one of the most sensitive measures to the effects of sleep loss (Basner & Dinges, 2011; D F Dinges et al., 1997; David F Dinges & Powell, 1985; Lim & Dinges, 2010). The PVT requires that subjects respond as quickly and accurately as possible to a visual stimulus presented at random inter-stimulus intervals on an electronic screen that provides response time feedback in milliseconds (ms), as well as an indication of a premature response [i.e., false start or error of commission]. The variable inter-stimulus interval (ISI) requires that subjects maintain sustained attention in order to achieve a high level of performance as defined by the following: (a) minimal number of lapses (i.e., RTs ≥ 500 ms indicative of errors of omission); (b) minimal number of false starts (i.e., premature responses [pre-stimulus onset] indicative of errors of commission; (Doran, Van Dongen, & Dinges, 2001; Lim & Dinges, 2008) (c) mean

response speed (RT msec/ 10^3); (d) mean fastest 10% RTs in ms; and (d) mean slowest 10% of RTs in ms, among other outcomes (Basner & Dinges, 2011). This task does not show any effect of aptitude, learning, or practice effects and is a sensitive measure of performance decline following sleep loss, reflected by increased RT, reduced speed, and greater number of lapses indicative of wake-state instability.

Doran et al (2001) observed increasing variability in the slopes of regression functions of neurobehavioral performance on the PVT across 88 hours of total sleep deprivation. In this and other studies of sleep deprivation, individuals showed slowed reaction speed and an increase in the number of attentional lapses from baseline, but the range of impairment varied among individuals, with the number of lapses after 36 hours of total sleep deprivation ranging between 6 and 100, and increases in reaction times from 10 milliseconds to more than 100 milliseconds (Baynard et al., 2003; Bliese, Wesensten, & Balkin, 2006). Van Dongen et al (2004) observed that some individuals, labeled as Type 1, show minimal performance deficits with sleep loss and often do not differ from individuals in the control condition who obtain a full night of sleep. Other individuals, identified as Type 3, appear to be extremely sensitive to sleep loss and show dramatic decrements in neurobehavioral performance early in a sleep deprivation or chronic sleep restriction protocol. These groupings often result from a tertile split of all study participants based on the change in PVT performance from baseline under the experimental condition. Data suggest these interpersonal differences represent a trait-like phenotypic response to sleep loss that remains stable over time. For a review of the literature on this phenotypic effect and potential biological mechanisms underlying interindividual vulnerability to sleep loss, see Tkachenko et al (2018).

Several potential mechanisms for observed interindividual differences have been proposed but none have yielded a comprehensive view of this phenomenon. Age may confer some resilience to performance decline under conditions of sleep loss, but this has only been observed when

comparing samples of a wide age range with limited effect among more homogenous, younger populations. Researchers have suggested that older adults are better able to maintain stable levels of performance due to reduced homeostatic sleep propensity during the circadian trough, related to changes in the sensitivity of the adenosinergic system that promotes build up of sleep pressure (Adam, Rétey, Khatami, & Landolt, 2006; Bliese et al., 2006; Landolt, Rétey, & Adam, 2012). Other demographic factors have not been associated with vulnerability to performance decline or subjective reports during sleep loss (Bliese et al., 2006; Frey, Badia, & Wright, 2004; William D Scott Killgore, Grugle, Reichardt, Killgore, & Balkin, 2009; Mallis et al., 2001; Satterfield, Wisor, Field, Schmidt, & Van Dongen, 2015; Van Dongen, Baynard, Maislin, & Dinges, 2004). A large literature on personality factors yields mixed findings, with some studies implicating extraversion, as well as neuroticism, trait anxiety, and several other traits, in performance decline and greater subjective sensitivity to the effects of sleep loss (Barbato et al., 2013; Blagrove & Akehurst, 2001; Carlozzi et al., 2010; Hill, Welch, & Godfrey, 1996; William D S Killgore, Richards, Killgore, Kamimori, & Balkin, 2007; Mastin, Peszka, Poling, Phillips, & Duke, 2005; Rupp, Killgore, & Balkin, 2010; Smith & Maben, 1993; D. J. Taylor & McFatter, 2003; Wu, Belenky, & Van Dongen, 2010). It has been also suggested that resilient individuals do not experience the same increase in homeostatic sleep pressure with extended time spent awake, and thus do not suffer from the same level of impairment as individuals with a more sensitive homeostatic process. The accumulation and dissipation of homeostatic sleep pressure during extended wakefulness so far has not been associated with changes in objective or subjective measures of performance (Aeschbach et al., 2001; Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014). However, it appears that individuals with habitually higher homeostatic sleep pressure may be predisposed to greater vulnerability to accumulating deficits with sleep loss (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014; Møst, E. I., Baynard, M. D., Fox, C. G., Blaauw, M. S., Ballas, C., Dinges, D. F., & Van Dongen, 2003).

To date, studies exploring potential predictors interindividual differences in response to sleep loss have relied on replication and relatively small sample sizes, yielding inconsistent findings. There is presently no single point of reference to document the significance, or lack thereof, of the impact of aforementioned variables on resilience to the effects of sleep loss. What follows is an examination of the relative impact of demographics, personality factors, and homeostatic sleep drive on interindividual differences in response to chronic partial sleep restriction in more than three hundred healthy adults. Chapter 1 conducts an exhaustive analysis of baseline variables, including personality, neurobehavioral performance, intellectual functioning, and demographics to examine potential factors associated with resilience or vulnerability to chronic partial sleep restriction. Chapter 2 investigates whether vulnerability groups differ in baseline homeostatic sleep pressure and habitual sleep patterns by examining sleep architecture and physiology at baseline as measured by polysomnography, and sleep timing and duration outside of the laboratory obtained by actigraphy monitoring. Chapter 3 examines whether vulnerability groups differ in the homeostatic response to five consecutive nights of sleep restriction to four hours time in bed using polysomnography measured across the protocol days. In addition to the discussions immediately following each chapter, an overall discussion is presented as the final chapter of the dissertation to integrate current findings in the context of known literature and propose future areas of research on this topic.

CHAPTER 2: METHODS

Participants

A total of N=306 healthy individuals (aged 21-50, n=128 females) participated in one of three laboratory studies used in these analyses. Subjects were $31.1y \pm 7.8y$ old (Mean $\pm$ SD), with an average BMI of 24.9 ± 3.5 . Forty-six percent were female, and 63.1% self-identified as minorities. Individuals were required to have typical wake times between 0600h and 0800h with no habitual napping or sleep disturbances. They were screened for medical or psychological conditions that would preclude participation, as well as drug and alcohol use, via clinical interviews, questionnaires, physical exams, and blood and urine tests. Individuals were excluded on the basis of recent drug use, a history of brain injury, irregular sleep/wake routines, or engagement in shift work or transmeridian travel in the past 2 months. Subjects abstained from caffeine, alcohol, tobacco, and medications (excluding birth control), for the week prior to the laboratory phase. During this week, participants were also monitored with actigraphy, sleep diaries, and time-stamped phone records for time in and out of bed. Out of 331 eligible participants, n=25 (8.9%) did not complete the protocol (n=19 withdrew due to personal reasons, n=3 were withdrawn for non-compliance or inability to perform the neurobehavioral tasks, and n=3 were withdrawn due to eligibility issues, including a positive pregnancy test after initiation of laboratory protocol).

Experimental Design

The present data were derived from three independent chronic sleep restriction experiments that required between 11 and 19 consecutive days under controlled laboratory conditions in the Sleep and Chronobiology Isolation Laboratory as part of the Clinical Translational Research Center of the Hospital of the University of Pennsylvania. Nurses performed daily clinical checks on all participants, and a physician was informed of any clinical issue. The final cohort of N=306

participants completed the protocol in groups of $n=3$ to 5 at a time. A total of $N=278$ were randomized to 5 nights of sleep restriction (SR), while $N=28$ were randomized to no sleep restriction (control condition). Both conditions received 2 baseline nights (B1, B2) of 10h time in bed (TIB) each night. Control subjects continued to receive 10h TIB each night for the remainder of the protocol, while sleep-restricted subjects underwent 5 nights (SR1-SR5) of restricted sleep opportunity limited to 4h TIB (0400h-0800h). The remaining days of each study involved conditions not reported here. Subjects obtained a final night of 10h TIB prior to departure from the laboratory, and continued to be monitored with actigraphy and sleep-wake diaries for one week.

Subjects randomized to the control condition underwent all of the same procedures as the sleep-restricted subjects, with the exception of neurobehavioral testing during times they were asleep and the sleep-restricted subjects remained awake (i.e., 2200h-0400h). All participants were continuously monitored by trained research staff to ensure adherence to the protocol. On days B2, SR1, and SR5, subjects wore ambulatory physiological recording equipment throughout the day (EEG) and night (PSG). On days without physiological monitoring, subjects were permitted to shower between 1430h and 1600h. Regular meals were provided throughout the protocol (0830h-1000h, 1230h-1400h, 1830h-2000h). Laboratory lighting was kept constant at <50 lux during periods of scheduled wakefulness and <1 lux during scheduled sleep times. Temperature was kept between 22° and 24° C.

Beginning at 0800h on each day of the protocol, subjects completed 30-min bouts of computerized neurobehavioral assessments every 2h during scheduled wakefulness. For the purposes of these analyses, overall daytime performance was determined by averaging the test bouts between 1000h and 1900h each day. This ensures that all subjects contribute to all time points and that results are relevant to a midday period of functioning and not overly influenced by the effects of different circadian phases and sleep inertia (Mollicone, Van Dongen, Rogers, Banks, & Dinges, 2010). Between test bouts, participants were free to watch television and

movies, play games, read, or interact with staff/other participants to remain awake. No naps or vigorous physical activities were permitted. All subjects were compensated for their time. The protocol was approved by the Institutional Review Board of the University of Pennsylvania.

The primary outcome measure is the Psychomotor Vigilance Test (PVT), a sustained-attention, reaction-time-based, measure of vigilant attention that has been extensively validated for its sensitivity to sleep loss (Chua, Yeo, Lee, Tan, Lau, Tan, et al., 2014; Kuna et al., 2012; Van Dongen, Dijkman, Maislin, & Dinges, 1999). It reveals deficits in psychomotor speed, vigilance, errors of omission and commission, time-on-task decrements, and wake state instability as a function of sleep loss and circadian phase. To perform the task participants press the computer keyboard “space” bar as quickly as possible in response to a visual stimulus presented on the screen every 2-10 seconds (random interstimulus interval) for a total of 10 minutes. The primary outcomes for the PVT were the total number of lapses of attention (defined as the number of times the reaction time exceeded 500ms), total number of false starts or preemptive responses, and the average of the fastest 10% of RTs for each session. Studies have categorized individuals as vulnerable or resilient to the effects of sleep loss based on a tertile split of the change in raw PVT lapses (RT >500ms) from baseline following 5 nights of sleep restriction (Van Dongen et al., 2004). In the present study, this yielded n=93 individuals in the Type 1 (resilient) group, n=93 individuals in the Type 3 (vulnerable) group with the greatest increase in the number of lapses, as well as n=92 individuals in the intermediate range of performance change following sleep restriction (Type 2).

CHAPTER 3: BASELINE NEUROBEHAVIORAL MEASURES AND VULNERABILITY TO SLEEP RESTRICTION

Introduction

The underlying mechanisms of phenotypic vulnerability to sleep loss are poorly understood. Numerous factors have been used in an attempt to account for the large inter-individual differences but none have yielded a comprehensive view of this phenomenon. If inter-individual vulnerability to the effects of sleep restriction is measured by performance on a single neurobehavioral measure, performance on that same measure during a rested condition may offer information about individual response to subsequent sleep loss. Baseline differences in performance on neurobehavioral tasks have been shown to account for a large portion of the between-subject variance on several tasks, including the PVT (Gunzelmann, Moore, Gluck, Dongen, & Dinges, 2009; Van Dongen et al., 2004). Chua and colleagues reported that despite highly stable individual differences in PVT performance across 2 sessions of 26h TSD as measured by intraclass correlation coefficients ($ICC=0.79-0.85$), much of the variance was accounted for by baseline performance (Chua, Yeo, Lee, Tan, Lau, Tan, et al., 2014). Individuals who are more vulnerable to the effects of sleep loss tend to have slower and more variable reaction times on the PVT at baseline (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014). Patanaik et al (2014) showed that vulnerable and resilient individuals differ in diffusion drift parameters derived from reaction times on the PVT at baseline, and later used drift diffusion model parameters to classify individuals in terms of vulnerability to total sleep deprivation with 77-82% accuracy. Thus far, the best predictor of impairment on the PVT following sleep loss is performance on the task while rested.

Age has failed to reliably predict change in performance under conditions of sleep loss (William D Scott Killgore et al., 2009; Mallis et al., 2001; Satterfield et al., 2015; Van Dongen et al., 2004). However, the majority of studies have focused on young adults, with participant age ranging from

late teens to mid-forties. Studies including older participants (61-70y) found that older subjects display more stable responses throughout 40h TSD, as evidenced by fewer lapses and smaller differences between the 10th and 90th percentiles of PVT speed (Adam et al., 2006). Although younger subjects had faster response speed during the baseline period, they demonstrated much larger reductions in average speed so that they were significantly slower than older participants around the circadian nadir. Landolt et al (2012) reported similar results and posited that this difference may be due to impaired sensitivity of the adenosinergic system. However, this hypothesis has not yet been directly tested. Older adults also show smaller declines in performance as measured by PVT reaction time during chronic partial sleep restriction, as compared with younger participants (Bliese et al., 2006; Zitting et al., 2018). One study noted the effect size was quite small, accounting for only 3% of the variance, and there was no significant interaction of age, severity of sleep restriction, and time in the protocol, suggesting age may have an impact on PVT performance in general and may not necessarily be a protective factor against the effects of sleep loss.

While other demographic factors including sex and race have been implicated with inter-individual differences in physiological response to sleep loss, they have not been associated with neurobehavioral vulnerability to sleep loss across single or repeated exposures to TSD or SR (Bliese et al., 2006; Frey et al., 2004; William D Scott Killgore et al., 2009; Mallis et al., 2001; Satterfield et al., 2015; Van Dongen et al., 2004). Self-reported chronotype, whether an individual's alertness levels tend to peak in the mornings ("larks") or evenings ("owls") as measured by the Morningness-Eveningness Questionnaire (MEQ), was shown to discriminate between average individuals and those resilient to the effects of sleep loss on PVT performance during TSD (J. A. Horne & Ostberg, 1976b). Resilient individuals were more likely to rate themselves as "owls" with a delayed circadian rhythm (Mallis et al., 2001). However, MEQ scores could not discriminate the most vulnerable subjects from those who were resilient, demonstrating its limited predictive power. While subjective reports of mood did not differ between morning and

evening types at baseline, morning types also showed a significant decline in subjective mood during TSD (Mallis et al., 2001). The relationship between self-reported chronotype and vulnerability to sleep loss has not yet been examined in the context of chronic partial sleep restriction.

The potential role of intelligence or academic achievement in resilience to sleep loss has also not been explicitly addressed. Several publications state that interindividual differences are not accounted for by IQ, but do not provide direct evidence in support of the claim (Basner, Rao, Goel, & Dinges, 2013; Goel, 2011). Goel et al (2009) showed that individuals with different genotypes of the *PER3* gene, associated with cognitive decline following total sleep deprivation, did not differ in IQ as measured by the North American Adult Reading Test (Goel, Banks, Mignot, & Dinges, 2009). However, the same study failed to show differential response to chronic partial sleep restriction on the PVT among the three groups, and did not examine the relationship between IQ and PVT performance across sleep restriction.

A large literature on personality factors implicates extraversion, as well as neuroticism, trait anxiety, and several others, in performance decline and greater subjective sensitivity to the effects of sleep loss. Eysenck first suggested in the early to mid-50s that there may be a “constitutional difference” between introverts and extraverts, beyond socialization preferences (H. J. Eysenck, 1957). A series of experiments conducted to examine the impact of introversion and extraversion on performance demonstrated that introverts perform better on attention tasks during sleep deprivation, which was hypothesized to result from a difference in inherent levels of activation, such that introverts “occupy a higher level in the arousal continuum than extraverts” (Corcoran, 1972). Assuming that there is a U-shaped relationship between arousal and performance that may vary slightly by task, introverts were thought to be positioned closer to optimal performance at the outset, so that as sleep deprivation reduces both groups in arousal levels, the higher basal arousal of introverts allows them to maintain relatively spared

performance levels, while extraverts reach low enough levels of arousal to produce poor performance. While this theory accommodated the results of earlier studies, it has been complicated by findings showing differential fluctuations in arousal levels of introverts and extraverts by time of day, suggesting the need for further tests of the theory (M. W. Eysenck, 1988).

Studies of one night of TSD in the laboratory demonstrate greater performance decrements in subjects scoring high on extraversion across tasks measuring vigilance, logical reasoning, time estimation, working memory, and response inhibition (Smith & Maben, 1993; D. J. Taylor & McFatter, 2003). Across longer bouts of extended wakefulness, higher scores on extraversion predicted greater decline in performance as measured by PVT reaction speed and lapses across 77h TSD (William D S Killgore et al., 2007). However, this was only observed for the first night of TSD, as all subjects were equally impaired after the second and third night of wakefulness, suggesting that such a strong shock to the system yielded performance decline even in introverts who may otherwise be capable of tolerating sleep loss at less severe levels. Researchers failed to find any association between PVT performance during TSD and any of the other subscales on the NEO Personality Inventory (Costa & McCrae, 1992). Across repeated exposure to 36h TSD, higher scores on extraversion predicted fewer lapses on the PVT in one protocol, but there was no significant relationship between personality and PVT performance in the second (Wu et al., 2010). In a laboratory study of one night TSD, subjects who scored lower on extraversion on the Eysenck Personality Inventory (EPI) reported higher sleepiness, lower vigilance and activation, and lower mood rating, as well as greater decline in vigilance and mood over the course of sleep deprivation, compared with those who scored highly on extraversion (Barbato et al., 2013). Authors hypothesized that participants who are more extraverted tend to seek out more social stimulation from the research staff, which allows them to maintain higher levels of subjective mood during sleep loss.

This hypothesis was put to the test in a laboratory study of individuals characterized as extraverts or introverts based on a median split of EPI scores, across 36h TSD in which social stimulation was explicitly manipulated (Rupp et al., 2010). On the day prior to sleep deprivation, subjects spent 12 hours in either a socially enriched environment, with structured social group activities such as games, projects, or discussions, or an impoverished social environment, in which subjects engaged in similar types of activities but in relative isolation from other individuals. During the daytime, while the social exposure was implemented, there was no difference in performance on the PVT between subjects in the two personality groups or in the two social conditions. However, introverts in the socially enriched condition reported being less subjectively sleepy and were more alert as measured by the Maintenance of Wakefulness Test (MWT), suggesting that daytime sleepiness may be underestimated when individuals are in socially engaging situations (Schröder, 2010). There were no differences between the personality groups or social enrichment conditions on subjective sleepiness or alertness during the night. Following TSD, subjects characterized as extraverts showed “riskier” performance on measures of risk and decision-making, but no effect of social exposure earlier that day was observed (Rupp, Wesensten, & Balkin, 2012). On the PVT, extraverts who were in the socially enriched environment during the day showed greater declines in performance as compared with those who were in the socially impoverished environment, who did not differ significantly from the introverts. Authors hypothesized that extraverts may be more responsive to social enrichment, which might result in greater “use-dependent” fatigue of neuronal networks involved in cognitive functions (Rupp et al., 2010). Despite the relatively large literature on the influence of personality on cognitive performance during sleep loss, variability in study design, level of laboratory controls, and the metrics used to capture personality, as well as the lack of studies examining the influence of personality on performance across repeated exposures to sleep loss, make it difficult to unequivocally support any single personality factor as a reliable predictor of individual response.

While many studies declare that interindividual differences in response to sleep loss cannot be explained by baseline psychological or behavioral measures, there is currently no conclusive reference available for this claim. Given the large sample size and breadth of available information on participants, the dataset used in this analysis is uniquely able to investigate all of these potential factors in relation to individual vulnerability to the effects of sleep loss. The present study performs an exhaustive analysis of baseline variables available for a large sample of individuals to examine potential factors associated with change in PVT performance during chronic partial sleep restriction.

Methods

Measures

Psychomotor Vigilance Test (PVT) – The PVT is a reaction-time-based measure of vigilant attention that has been extensively validated for its sensitivity to sleep loss (Doran et al., 2001; Dorrian, Rogers, & Dinges, 2005; Lim & Dinges, 2008). It reveals deficits in psychomotor speed, vigilance, errors of omission and commission, time-on-task decrements, and wake state instability as a function of sleep loss and circadian phase. To perform the task participants press the computer keyboard “space” bar as quickly as possible in response to a visual stimulus presented on the screen every 2-10 seconds (random interstimulus interval) for a total of 10 minutes. The primary outcomes for the PVT were the per test bout total number of lapses of attention (defined as the number of times the reaction time exceeded 500ms), false starts, and the average of the fastest 10% of RTs for each session. Data were available for N=278 participants.

Digit Symbol Substitution Test (DSST) – The DSST is a 90-second computerized version of the Digit Symbol Substitution Task in the Wechsler Adult Intelligence Scale (Wechsler, 1997). Participants were presented with a table of 9 line symbols and associated numbers at the top of

the screen, and asked to respond as quickly and accurately as possible to a stimulus symbol, presented one at a time, by pressing the corresponding number key on the keyboard. A new stimulus symbol is presented as soon as a response to the last symbol is made. At each test bout, the pattern of symbol and digit pairs is selected at random from a set of 24 possible patterns, to reduce the possibility of practice effects. The primary outcome for this task was the total number of correct responses. Data were available for N=278 participants.

Digit Span Task (DGS) – The DGS is a computerized version of the Digit Span Task in the Wechsler Adult Intelligence Scale designed to measure working memory (Wechsler, 1997). Participants were presented with a series of digits, one at a time, after which they are asked to recall the entire series by entering the appropriate number keys. There are two versions of the task: in the forward digit-span task, subjects must enter the digits in the order presented on the screen, while in the backward digit-span task they must reverse the order of the numbers in the series. If a subject responds correctly, the length of the series is increased each time, to determine the maximum length that can be achieved. The four outcome measures for the task included the maximum length and total number correct in the forward and backward versions. Data were available for N=273 participants.

Profile of Mood States (POMS) – Subjects were asked to indicate how they felt at the moment relative to each of the 65 listed adjectives, using a 5-point Likert-type scale ranging from 1 (Not at all) to 5 (Extremely). This measure yields six main factors: tension, depression, anger, fatigue, vigor, and confusion. For this study, the main outcome measure was the subject's score on the fatigue scale (Douglas M. McNair, Maurice Lorr, 1971). Data were available for N=278 participants.

Karolinska Sleepiness Scale (KSS) – The KSS is a 9-point Likert-type scale on which subjects indicate their level of subjective sleepiness at the moment, ranging from 1 (very alert) to 9 (very

sleepy) (Torbjörn Åkerstedt & Gillberg, 1990; Nordin, Åkerstedt, & Nordin, 2013). Data were available for N=278 participants.

Visual-Analog Scale for Fatigue (VAS-F) – The VAS-F is a set of 18 analog mood scales in which subjects are asked about their feelings concerning energy and tiredness (Lee, Hicks, & Nino-Murcia, 1991; Shahid, Wilkinson, Marcu, & Shapiro, 2011). It was administered on the computer. Subjects used cursors to continuously move a marker along an un-indexed reference line from an initial central location to indicate how they felt in that moment relative to the descriptors printed at each end of the line. Data were available for N=278 participants.

Maintenance of Wakefulness Test (MWT) – The MWT is an objective laboratory based measure of the ability to stay awake (Doghramji et al., 1997; Littner et al., 2005; Mitler, Gujavarty, & Browman, 1982). It was administered at B2 and SR5 between 1400-1700h. Subjects were asked to remain awake as long as possible under soporific conditions, with a maximum time limit of 30 minutes. Wakefulness was monitored with EEG, EMG, and EOG. The primary outcome was the time to the first occurrence of a microsleep (10s of unambiguous sleep evidenced by EEG theta activity). Complete data for the MWT were available for N=212 participants.

Hayling Sentence Completion Test – The Hayling Test consists of two sets of 15 sentences, each missing the last word. Each sentence is read aloud by an examiner and individuals are asked to complete the sentence. In the first set of questions, individuals can complete the sentence with the first word that comes to mind. In the second set, individuals are asked to complete the sentence with a word that does not fit. Response latencies are recorded in seconds and converted to scaled scores. The test is a measure of response initiation and suppression and is often used as a proxy for executive functioning (Burgess & Shallice, 1996). Data were available for N=272 participants.

North American Adult Reading Test (NAART) – The NAART consists of 61 irregular words which are read aloud by the participant and scored for pronunciation accuracy according to American and Canadian standards. It is used as a measure of premorbid IQ (Friend & Grattan, 1998; Uttl, 2002). Primary outcome measures include Verbal IQ (VIQ), Performance IQ (PIQ), and Full Scale IQ (FSIQ). Due to high collinearity among the three outcome variables, only FSIQ was used in the present analyses. Complete data were available for N=272 participants.

Morningness-Eveningness Questionnaire (MEQ) - This is a 19-item self-assessment measure of the degree to which individuals are active and alert at different times of day. Scores can range from 16-86, with higher scores indicative of morning type (J. A. Horne & Ostberg, 1976b). Complete data for the MEQ were available for N=261 participants.

Eysenck Personality Inventory (EPI) – The EPI is a 57-item yes/no questionnaire designed to measure two dimensions of personality: extraversion and neuroticism. The instrument yields total scores for Neuroticism, Extraversion, Psychoticism, and a Lie/Desirability score that serves as a measure of validity (H. J. Eysenck & Eysenck, 1968; Howarth, 1976). Data were available for N=250 participants.

Subject Demographics – Several demographic variables were examined in relation to interindividual vulnerability to sleep loss. These include age, biological sex, ethnicity, body mass index (BMI), and depression symptomatology as indicated on the Beck Depression Inventory (BDI), a 21-item self-report inventory of depression symptoms (Beck, Steer, & Carbin, 1988). Data were available for age, sex, and ethnicity on N=278 participants, on the BDI for N=276 participants, and on BMI for N=268 participants.

Data Analysis

Data were visually examined to check for irregular patterns and severe outliers. Due to the low frequency of several ethnic categories on the demographic questionnaire, the variable was dichotomized into those who self-identified as Caucasian and Non-White, which included African American, Asian, Hispanic, Native Hawaiian/Pacific Islander, and more than one ethnicity. The primary outcome variable of change in PVT lapses was severely skewed to the right. Data were transformed with a cubed root function ($x^{1/3}$) to retain information about directionality of change over time. Due to significant collinearity among the four outcomes for the Digit Span Task, a Principal Components Analysis (PCA) was performed to create a single composite index to reflect overall performance on this task. Severely skewed distributions were also observed for PVT raw lapses, PVT false starts, and the POMS-Fatigue scale. A reciprocal transformation ($1/(x+1)$) was applied to these data. Distribution of VAS-F responses showed severe rightward skew with a possible floor effect for the scores. These data were transformed with a $\log_{10}(x+1)$ function. Lastly, the MWT data showed significant leftward skew along with a clear ceiling effect. Thirty-five percent of the participants achieved the maximum score, indicative of their ability to remain awake for entire duration of the test. Therefore, the data were dichotomized to indicate whether or not each individual was able to remain awake during the test. The remaining variables were reasonably normally distributed with no concerning outliers.

Patterns of missing data among all independent variables are shown in Figure 1. Data for the MWT were missing for 23.7% of participants (N=66). It was assumed to be missing at random (MAR) as the measure was not collected for one of the three studies from which the data were pooled. The EPI data were missing for 10.1% (N=28) of participants. Data on the MEQ were unavailable for 6.1% (N=17) of participants. Less than 4% of data were missing for the BMI, NAART, Hayling, and the Digit Span Task.

[Figure 1 here]

Three separate analyses targeting the research question were conducted using listwise deletion, multiple imputation, and full information maximum likelihood estimation to account for missing data. Independence of residuals was confirmed by a Durbin-Watson statistic of 1.936. Homoscedasticity and linearity were assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by partial correlations below 0.70 among the independent variables and tolerance values greater than 0.45. Casewise diagnostics noted 3 outliers based on studentized deleted residuals greater than ± 3 standard deviations. These cases were nevertheless included in the model as they were deemed to be within the expected range of values on each measure. There were no leverage values greater than 0.2 or values for Cook's distance above 1. Normality of residuals was confirmed with visual inspection of the histogram of residuals as well as the Normal P-P Plot of regression standardized residuals.

Listwise deletion. A hierarchical regression analysis was conducted on the complete dataset to examine baseline variables associated with change in PVT lapses across five consecutive nights of sleep restriction over and above baseline PVT performance alone. The regression was run using the Statistical Package for Social Sciences (SPSS) version 24.0 for Macintosh (IBM Corp., 2016). Missingness was treated with listwise deletion, resulting in a final sample of N=161 participants with complete data on all variables of interest. Independent variables were introduced into the model in predetermined blocks as indicated below (Models 1-7):

Model 1: Δ PVT Lapses ~ PVT Performance [Baseline Performance]
*Model 2: * ~ * + DSST + Digit Span [Neurobehavioral Performance]*
*Model 3: * ~ * + Maintenance of Wakefulness Test [Physiological Wakefulness]*
*Model 4: * ~ * + KSS + POMS + VAS [Subjective Reports]*
*Model 5: * ~ * + MEQ + Sex + Age + Ethnicity + BMI [Demographics]*
*Model 6: * ~ * + EPI [Personality]*
*Model 7: * ~ * + NAART + Hayling [Academic Intelligence]*

Multiple imputation. Multiple imputation (MI) performs well in small samples and even with large multiple regression models, with as much as 50% missing data (Graham, 2009). MI was applied

in SPSS (Version 24.0; IBM Corp., 2016) to address missing data, using predictive mean matching (PMM) with 50 maximum iterations (random seed=95). All analysis variables were used as predictors under the assumption that data are missing at random. For any variables with severely skewed distributions, transformations were conducted prior to MI as suggested by von Hippel et al (2009). Forty imputed datasets were generated based on recommendations by Graham et al (2007). The resulting dataset containing the original data with missing cases along with the 40 imputed complete datasets was imported into R version 3.5.1 using the 'foreign' package (R Core Team, 2018b, 2018a). Seven sequential multiple linear regression models on each imputed dataset were conducted using the 'mice' package in R, with independent variables introduced in predetermined blocks as previously indicated (Models 1-7) (van Buuren & Groothuis-Oudshoorn, 2011). Analyses run on each dataset were pooled according to Rubin's rules (Rubin, 1987). Pooled F and R^2 values were obtained using the R code provided by Ginkel et al (2019) and 'pool.r.squared' command in the 'mice' package, respectively (van Buuren & Groothuis-Oudshoorn, 2011).

Maximum Likelihood Estimation. Seven sequential linear regression models were conducted using the MIXED procedure in SPSS version 24.0 to take advantage of maximum likelihood estimation via an expectation-maximization algorithm for missing data (IBM Corp., 2016). Independent variables were introduced into the model in predetermined blocks as previously indicated (Models 1-7). Variable blocks that did not significantly improve the model as indicated by changes in -2 Log Likelihood, Akaike's information criterion (AIC), and Bayesian information criterion (BIC) metrics, were excluded from subsequent models (Burnham & Anderson, 2004).

Results

Demographic information for the present sample is shown in Tables 1 and 2. Participants ranged in age from 21-50 years (Mean=31.0, SD=7.8), and the sample was evenly split in terms of

biological sex (46% female). Approximately 38% of participants self-identified as Caucasian, 53% identified as African American, and almost 9% identified as either Asian, Hispanic, or more than one race. On average, participants had a BMI of 24.8 (range 16.3-32.6), a BDI score of 1.4 (range 0-12), and an MEQ score of 40.1 (range 26-55). Baseline performance on all measured variables averaged across vulnerability groups is displayed in Table 3.

[Tables 1, 2, and 3 here]

Listwise Deletion. See Table 4 for full details of each regression model. The full model including all baseline measures of interest was statistically significant, $R^2=0.24$, $F(20,140)=2.18$, $p=0.005$; adjusted $R^2=0.13$. The addition of neurobehavioral performance measures (DSST, Digit Span; Model 2) did not lead to significant improvement of the model beyond that accounted for by baseline PVT performance, ΔR^2 of 0.023, $F(2,155)=1.95$, $p=0.15$. The addition of performance on the MWT (Model 3) led to a statistically significant increase in R^2 of 0.027, $F(1,154)=4.783$, $p=0.03$. The addition of subjective reports of sleepiness and fatigue (Model 4) did not significantly improve the model, ΔR^2 of 0.005, $F(3,151)=0.29$, $p=0.83$. The addition of demographic variables (Model 5) led to a statistically significant increase in R^2 of 0.064, $F(5,146)=2.33$, $p=0.045$. Inclusion of personality (Model 6; ΔR^2 of 0.031, $F(4,142)=1.46$, $p=0.22$) and academic achievement (Model 7; ΔR^2 of 0.005, $F(2,140)=0.50$, $p=0.61$) did not significantly improve the model. A final multiple regression model was run, limiting the analysis to the three variable blocks found to be significant in hierarchical regression modeling. This model included baseline PVT performance, MWT performance, and demographics as predictor variables and was conducted on $N=196$ subjects with complete cases on all variables of interest. The model was statistically significant, $R^2=0.37$, $F(9,186)=3.34$, $p=0.001$, adjusted $R^2=0.10$. Increased lapses across five nights of sleep restriction were significantly associated with PVT lapses at baseline ($t=-2.8$, $p=0.006$) and baseline MWT ($t=-2.6$, $p=0.009$).

[Table 4 here]

Multiple Imputation. Pooled results for multiple linear regressions run on each of the 40 imputed datasets are shown in Table 5. The full model including all baseline measures of interest was statistically significant for the pooled analyses, $R^2=0.17$, $F(10,1046016)=2.38$, $p=0.0005$; adjusted $R^2=0.10$. Only the addition of MWT performance (Model 3) significantly improved fit, $\Delta R^2=0.033$, $F(1, 519893820)=10.268$, $p=0.001$. None of the other models resulted in significant model improvement ($p>0.30$). A final multiple regression model was run, limiting the analysis to baseline PVT performance and MWT. The model was statistically significant, $R^2=0.13$, $F(4, \text{Inf.})=10.36$, $p<0.001$, adjusted $R^2=0.12$. Increased lapses across five nights of sleep restriction were significantly associated with PVT lapses at baseline ($t=-4.0$, $p<0.001$) and baseline MWT ($t=-3.28$, $p=0.001$).

[Table 5 here]

Maximum Likelihood Estimation. Indices of model fit comparing the sequential models are shown in Table 6. The addition of subjective reports of sleepiness and fatigue did not yield any new information in the model (Model 4) as indicated by increased AIC and BIC values. Baseline scores on the POMS ($t=-0.01$, $p=0.99$), the KSS ($t=0.07$, $p=0.95$), and VAS-F ($t=-1.2$, $p=0.23$) were not associated with change in PVT lapses after five nights of sleep restriction. These variables were excluded from Models 5-7. The final model incorporating all of the variables with the exception of subjective reports was the best fit ($AIC=414.3$, $BIC=472.8$). Change in PVT lapses was significantly associated with baseline PVT lapses ($t=-2.36$, $p=0.02$), performance on the DSST ($t=-2.36$, $p=0.02$), and age ($t=-2.05$, $p=0.04$). Performance on the MWT did not reach statistical significance for predicting change in PVT performance during sleep restriction ($F(1,161)=3.6$, $p=0.06$).

[Table 6 here]

Discussion

The purpose of this study was to conduct an exhaustive analysis of baseline variables available for a large sample of individuals to examine potential factors associated with resilience or vulnerability to chronic partial sleep restriction. Multiple linear regression using listwise deletion found that the number of PVT lapses at baseline, performance on the MWT, and demographics, specifically age, significantly improved the model for change in PVT performance with sleep restriction. When these three sets of variables were run in a single model, only PVT lapses and MWT were significant, while age no longer reached significance. The same analysis using multiple imputation for missing data yielded similar results, with baseline PVT lapses and MWT performance as significant predictors of vulnerability to sleep loss. When maximum likelihood estimation was used to account for missing data, baseline PVT lapses were still identified as significant predictors of PVT performance change with sleep restriction. Other significant predictors of vulnerability to sleep loss included performance on the DSST and age.

Performance on the MWT did not reach statistical significance with maximum likelihood estimation. This finding should be considered in light of the fact that the majority of the missing data was attributed to this variable. Furthermore, while the addition of personality factors and intelligence measures improved the model as indicated by smaller AIC and BIC values, none of these measures were significant predictors of performance in the last two models (Models 6 & 7). If those sets of variables are removed from the final model, MWT performance remains statistically significant ($F(1,191)=5.9, p=0.016$). With that in mind and given the results of analyses using listwise deletion and multiple imputation, the ability to maintain wakefulness while rested as measured by the MWT should be further investigated as a possible predictor of resilience to sleep loss.

Frey et al (2004) showed that sleep latency on the MWT was much faster for the five most vulnerable participants, who fell asleep almost 8 minutes faster than the five most resilient individuals following total sleep deprivation. However, the study failed to observe any differences between the two groups on the MWT at baseline, likely due to the small sample size and the maximum duration of the MWT capped at 15 minutes. Such a short window of time creates a ceiling effect with limited inter-individual variability in performance, particularly in light of the normative data for the 40 minute MWT showing an average sleep latency of 35 minutes for healthy individuals (Doghramji et al., 1997). The concern of a ceiling effect is apparent in the present study as well, as 35% of the sample remained awake for the full 30 minutes of the task. Future investigations of wakefulness and its role in resilience to sleep loss would benefit from longer sleep windows on the MWT to unpack potentially valuable information on inter-individual differences in the ability to sustaining wakefulness beyond 30-40 minutes. Alternatively, researchers should consider utilizing increasingly soporific conditions for the MWT in order to pull for the ability to maintain wakefulness despite external cues and heightened sleep pressure.

Lastly, there is some indication that older participants and those with better performance on the DSST at baseline have fewer lapses of attention during sleep restriction, but results varied depending on how the analyses handled missing data. Age may confer some resilience to performance under conditions of sleep loss, but this has previously only been observed when comparing samples of a wide age range with limited effect among more homogenous, younger populations, as is the case in the present study. An earlier study examined the effects of 40h TSD on two separate occasions – with either placebo or 200mg of caffeine administration at 11h and 23h of wakefulness – in younger and older adults (Landolt et al., 2012). Results showed that sleep deprivation had the greatest impact on young subjects who were self-reported to be caffeine sensitive, with older and caffeine-insensitive younger subjects showing smaller deficits on PVT performance and subjective measures. While caffeine administration improved subjective

sleepiness across all subjects, there was a differential effect among the three groups on PVT performance. Caffeine improved performance only in those subjects self-identified as caffeine-sensitive, and did not attenuate the effects of sleep loss in older or caffeine-insensitive subjects. Authors suggest that impaired sensitivity of the adenosinergic system in older subjects may underlie the reduced effects of sleep deprivation on performance and homeostatic pressure. There is a need to examine the effect of aging on adenosine receptor functioning to investigate whether these changes account for any observed effect of age on vulnerability to sleep loss.

The present study did not find a significant effect of biological sex on vulnerability to sleep loss as measured by change in PVT performance. Recent findings have highlighted the effect of menstrual phase in females on cognitive performance during extended wakefulness. Women in the follicular phase showed greater lapses of attention on the PVT as compared with those in the luteal phase, with more than 60% of their responses exceeding 500ms in reaction times (Vidafar et al., 2018). These findings are consistent with other research showing worse performance on cognitive tasks during sleep deprivation in women in the follicular phase (Wright & Badia, 1999). Authors note that women in the follicular phase may show an increase in PVT lapses with extended wakefulness, while those in the luteal phase may demonstrate fewer lapses, relative to men. They caution that collapsing the menstrual phase groups may lead to inaccurate conclusions as any differences in performance are averaged out. The present analysis did not include information on menstrual phase for the female participants, which may have contributed to the lack of findings on gender effects. Future studies would benefit from examining menstrual phase in females as an additional factor, rather than controlling for the effect by limiting study participation to women in a specific menstrual phase or on contraceptives.

In sum, the present analyses replicated prior research showing baseline PVT performance is predictive of change in performance on the task under conditions of sleep loss. Individuals with more lapses of attention on the PVT at baseline showed greater impairment on the task under

chronic partial sleep restriction. Additionally, results suggest that individuals who were unable to remain awake for the entire duration of the MWT at baseline had larger increases in PVT lapses after five nights of sleep restriction. The impact of age on vulnerability to sleep loss requires further investigation, as the present study yielded varying conclusions based on choice of statistical methods. This was the first study to examine the relationship between self-reported chronotype and vulnerability to the effects of chronic partial sleep restriction. Results indicate no impact of subjective morningness-eveningness on change in PVT performance during sleep restriction. There was also no evidence for a significant impact of demographic characteristics, subjective reports of mood, personality, or intelligence on vulnerability to five consecutive nights of chronic partial sleep restriction as measured by change in PVT performance.

Table 1. Demographic characteristics of study participants by vulnerability type. Means and standard deviations for age, body mass index, morningness-eveningness scores, and depression ratings by group.

	Vulnerability Type					
	Type 1		Type 2		Type 3	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
Age (yrs)	31.95	7.92	31.90	8.14	29.22	7.11
BMI ^a	24.40	3.45	25.21	3.62	24.82	3.66
MEQ ^b	40.23	6.12	40.17	6.40	39.82	5.38
BDI ^c	1.10	1.79	1.31	2.03	1.74	2.43

^aBody Mass Index (BMI)

^bMorningness-Eveningness Questionnaire

^cBeck Depression Inventory

Table 2. Demographic characteristics by vulnerability type – counts of sex and ethnicity by group.

		Vulnerability Type					
		Type 1		Type 2		Type 3	
		N	%	N	%	N	%
Sex	<i>Male</i>	46	49.5	53	57.6	51	54.8
	<i>Female</i>	47	50.5	39	42.4	42	45.2
Ethnicity	<i>Caucasian</i>	34	36.6	36	39.1	35	37.6
	<i>African American</i>	54	58.1	47	51.1	48	51.6
	<i>Other^a</i>	5	5.4	9	9.8	10	10.8

^aEncompasses individuals self-identified as Asian, Hispanic, Native Hawaiian/Pacific Islander, and more than one ethnicity.

Table 3. Baseline performance on all independent measures by vulnerability type. Means and standard deviations by group.

	Vulnerability Type					
	Type 1		Type 2		Type 3	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
PVT Raw Lapses ^a	1.26	2.58	1.80	2.16	3.41	4.31
PVT Fastest 10% RT (ms) ^a	198.84	21.14	200.83	18.55	205.21	20.69
PVT False Starts ^a	1.26	1.72	1.53	1.82	1.58	1.58
DSST # Correct ^b	58.57	8.09	55.62	9.78	54.74	8.93
DS-Forward # Correct ^c	5.76	1.28	5.63	1.28	5.38	1.20
DS-Forward Max ^c	6.87	1.17	6.74	1.18	6.58	1.03
DS-Back # Correct ^c	5.05	1.78	4.77	1.76	4.25	1.51
DS-Back Max ^c	6.20	1.65	5.90	1.64	5.55	1.51
MWT (min) ^d	22.92	9.42	21.77	9.28	16.71	10.29
KSS ^e	2.97	1.37	2.97	1.25	3.22	1.30
POMS-Fatigue ^f	0.93	1.40	0.73	1.20	0.62	4.90
VAS Exhausted/Energetic ^g	33.64	34.97	26.47	31.79	12.58	20.76
EPI Extraversion ^h	15.10	3.58	15.25	4.28	15.71	3.66
EPI LieDesirability ^h	12.59	4.14	12.55	4.01	11.44	4.26
EPI Neuroticism ^h	5.30	2.34	5.31	2.32	5.57	2.25
EPI Psychoticism ^h	2.71	1.70	2.93	1.80	2.93	1.81
NAART FSIQ ⁱ	105.34	8.82	103.68	8.35	104.55	9.12
Hayling Scaled Total ^j	5.49	1.45	5.26	1.47	5.30	1.40

^aPsychomotor Vigilance Test (PVT)

^bDigit Symbol Substitution Test (DSST)

^cDigit Span Test (DS)

^dMaintenance of Wakefulness Test (MWT)

^eKarolinska Sleepiness Scale (KSS)

^fProfile of Mood States – Fatigue (POMS-F)

^gVisual Analogue Scale (VAS)

^hEysenck Personality Inventory (EPI)

ⁱNorth American Adult Reading Test (NAART)

^jHayling Sentence Completion Test (Hayling)

Table 4. Model parameters and fit using hierarchical regression with listwise deletion.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Fixed Effects	<i>Estimate β</i>		<i>Estimate β</i>		<i>Estimate β</i>		<i>Estimate β</i>		<i>Estimate β</i>		<i>Estimate β</i>		<i>Estimate β</i>	
<i>Intercept</i>	2.56*		3.47**		3.58**		3.59**		3.81*		2.80*		3.62	
<i>PVT Lapses</i>	-0.91**	-0.29	-0.86*	-0.27	-0.82*	-0.26	-0.73*	-0.23	-0.60*	-0.19	-0.58	-0.18	-0.53	-0.17
<i>PVT False Start</i>	-0.11	-0.03	-0.10	-0.03	-0.10	-0.03	-0.11	-0.03	-0.13	-0.04	-0.06	-0.02	-0.04	-0.01
<i>PVT Fastest 10% RT</i>	-0.003	-0.06	-0.003	-0.07	-0.004	-0.08	-0.003	-0.06	0.001	0.02	0.002	0.05	0.003	0.05
<i>DSST # Correct</i>			-0.02	-0.16	-0.01	-0.15	-0.02*	-0.16	-0.02*	-0.22	-0.02*	-0.20	-0.02*	-0.19
<i>Digit Span</i>			-0.02	-0.04	-0.03	-0.07	-0.04	-0.08	-0.01	-0.03	-0.01	-0.02	-0.02	-0.03
<i>MTT</i>					-0.30*	-0.17	-0.29*	-0.16	-0.26	-0.14	-0.24	-0.13	-0.23	-0.13
<i>KSS</i>							0.01	0.02	0.02	0.02	0.004	0.006	0.003	0.005
<i>POMS</i>							-0.04	-0.01	-0.13	-0.04	-0.18	-0.06	-0.20	-0.07
<i>VAS-Fatigue</i>							-0.14	-0.07	-0.12	-0.06	-0.10	-0.05	-0.17	-0.08
<i>Sex</i>									-0.21	-0.12	-0.23	-0.13	-0.22	-0.12
<i>Age</i>									-0.02*	-0.20	-0.02	-0.16	-0.02	-0.16
<i>Ethnicity</i>									-0.18	-0.10	-0.10	-0.06	-0.14	-0.07
<i>MEQ</i>									-0.006	-0.04	-0.003	-0.02	-0.002	-0.01
<i>BMI</i>									0.03	0.13	0.03	0.12	0.03	0.11
<i>EPI Extraversion</i>											0.03	0.13	0.03	0.13
<i>EPI Lie/Desirability</i>											-0.02	-0.09	-0.02	-0.12
<i>EPI Neuroticism</i>											0.06	0.13	0.05	0.12
<i>EPI Psychoticism</i>											-0.03	-0.06	-0.03	-0.07
<i>Hayling Scaled Score</i>													-0.04	-0.07
<i>NAART</i>													-0.005	-0.05
Model Fit														
R^2	0.08		0.11		0.13		0.14		0.20		0.23		0.24	
F	4.71		3.64		3.90		2.66		2.62		2.39		2.18	
ΔR^2	0.08		0.02		0.03		0.005		0.06		0.03		0.005	
ΔF	4.71		1.95		4.78		0.29		2.33		1.46		0.50	
<i>Sig. ΔF (p-value)</i>	0.004		0.15		0.03		0.83		0.045		0.22		0.61	

N=161

*p<0.05

**p<0.001

Table 5. Model parameters and fit using sequential linear regression with multiple imputation.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	<i>Std.</i>		<i>Std.</i>		<i>Std.</i>		<i>Std.</i>		<i>Std.</i>		<i>Std.</i>		<i>Std.</i>	
Fixed Effects	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>	<i>Estimate</i>	<i>Error</i>
<i>Intercept</i>	2.569**	0.668	3.075**	0.745	3.054**	0.733	2.979**	0.765	2.866*	1.057	2.357*	1.154	3.158*	1.600
<i>PVT Lapses</i>	-1.059**	0.233	-0.993**	0.247	-0.889**	0.245	-0.780*	0.263	-0.686*	0.274	-0.689*	0.276	-0.676*	0.277
<i>PVT False Start</i>	-0.213	0.254	-0.201	0.255	-0.193	0.251	-0.217	0.252	-0.142	0.262	-0.092	0.265	-0.057	0.267
<i>PVT Fastest 10% RT</i>	-0.022	0.003	-0.002	0.003	-0.002	0.003	-0.002	0.003	-0.001	0.003	-0.001	0.004	-0.001	0.004
<i>DSST # Correct</i>			-0.010	0.006	-0.009	0.006	-0.010	0.006	-0.014*	0.007	-0.013	0.007	-0.012	0.007
<i>Digit Span</i>			-0.006	0.034	-0.014	0.034	-0.021	0.034	-0.019	0.037	-0.016	0.037	-0.023	0.039
<i>MWT</i>					-0.373*	0.117	-0.359*	0.120	-0.327*	0.126	-0.313*	0.127	-0.312*	0.127
<i>KSS</i>							0.039	0.050	0.048	0.053	0.036	0.054	0.037	0.054
<i>POMS</i>							0.098	0.220	0.164	0.226	0.128	0.227	0.133	0.229
<i>VAS-Fatigue</i>							-0.153	0.144	-0.154	0.153	-0.130	0.158	-0.172	0.163
<i>Sex</i>									-0.048	0.124	-0.054	0.125	-0.050	0.125
<i>Age</i>									-0.010	0.008	-0.008	0.008	-0.007	0.008
<i>Ethnicity</i>									-0.106	0.129	-0.051	0.124	-0.084	0.138
<i>MEQ</i>									0.002	0.011	0.004	0.011	0.004	0.012
<i>BMI</i>									0.017	0.017	0.017	0.017	0.016	0.017
<i>EPI Extraversion</i>											0.022	0.016	0.022	0.016
<i>EPI Lie/Desirability</i>											-0.019	0.016	-0.023	0.016
<i>EPI Neuroticism</i>											0.023	0.027	0.020	0.028
<i>EPI Psychoticism</i>											-0.011	0.035	-0.013	0.035
<i>Hayling Scaled Score</i>													-0.042	0.043
<i>NAART</i>													-0.004	0.009
Model Fit														
<i>R²</i>	0.098		0.106		0.139		0.145		0.148		0.162		0.167	
<i>F</i>	9.880		6.368		7.197		5.004		3.102		2.581		2.384	
ΔR^2	0.098		0.008		0.033		0.006		0.003		0.014		0.005	
ΔF	9.880		1.204		10.268		0.644		0.613		0.914		0.699	
<i>Sig. ΔF (p-value)</i>	<0.001		0.300		0.001		0.587		0.690		0.455		0.497	

*p<0.05

**p<0.001

Table 6. Model parameters and fit using sequential linear regression with maximum likelihood estimation.

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>Estimate</i>	<i>Std. Error</i>
Fixed Effects														
<i>Intercept</i>	2.57**	0.66	3.35**	0.73	2.75**	0.83	2.70*	0.87	2.98*	1.16	2.29*	1.33	2.33	1.80
<i>PVT Lapses</i>	-1.06**	0.23	-1.11**	0.24	-0.92**	0.25	-0.80*	0.27	-0.76*	0.26	-0.64*	0.27	-0.64*	0.27
<i>PVT False Start</i>	-0.21	0.25	-0.14	0.25	-0.20	0.27	-0.21	0.27	-0.17	0.28	-0.17	0.29	-0.02	0.29
<i>PVT Fastest 10% RT (ms)</i>	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<i>DSST # Correct</i>			-0.01	0.01	-0.01*	0.01	-0.01*	0.01	-0.02*	0.01	-0.02*	0.01	-0.02*	0.01
<i>Digit Span</i>			-0.01	0.03	-0.03	0.03	-0.04	0.04	-0.01	0.04	-0.01	0.04	-0.01	0.04
<i>MWT</i>					0.36*	0.12	0.34*	0.12	0.30*	0.12	0.26	0.13	0.25	0.13
<i>KSS</i>							0.00	0.05	.	.	.	.	.	.
<i>POMS</i>							0.00	0.24	.	.	.	.	.	.
<i>VAS-Fatigue</i>							-0.17	0.14	.	.	.	.	.	.
<i>Sex</i>									0.19	0.13	0.19	0.13	0.18	0.14
<i>Age</i>									-0.02*	0.01	-0.02*	0.01	-0.02*	0.01
<i>Ethnicity</i>									0.11	0.14	0.14	0.15	0.12	0.16
<i>MEQ</i>									-0.01	0.01	0.00	0.01	0.00	0.01
<i>BMI</i>									0.01	0.02	0.02	0.02	0.03	0.02
<i>EPI Extraversion</i>											0.03	0.02	0.03	0.02
<i>EPI Lie/Desirability</i>											-0.02	0.02	-0.02	0.02
<i>EPI Neuroticism</i>											0.05	0.03	0.06	0.03
<i>EPI Psychoticism</i>											-0.03	0.04	-0.03	0.04
<i>Hayling Scaled Score</i>													-0.04	0.05
<i>NAART</i>													0.00	0.01
Model Fit														
<i>-2 Log Likelihood</i>	737.59		706.46		514.21		509.30		459.93		395.34		376.28	
<i>AIC</i>	747.59		720.46		530.21		531.30		485.93		429.34		414.28	
<i>BIC</i>	765.73		745.72		556.87		567.86		528.21		482.35		472.83	
<i>Residual</i>	0.83		0.78		0.70		0.70		0.65		0.62		0.61	
<i>*p < 0.05</i>														
<i>**p < 0.001</i>														

Figure 1. Missing data among all independent variables. Set size displayed on the bottom left axis reports total number of missing data points for each variable. Histogram shows incidence of missing data points for various combinations of variables as indicated by the dark circles connected by lines.

CHAPTER 4: EFFECTS OF HABITUAL SLEEP PATTERNS AND BASELINE HOMEOSTATIC SLEEP PRESSURE ON RESPONSE TO CHRONIC PARTIAL SLEEP RESTRICTION

Introduction

Healthy human sleep comprises two states – rapid eye movement (REM) and non-REM sleep that alternate cyclically across a sleep episode. These state characteristics are well-defined and can be observed in electrical brain activity and measured using polysomnographic electroencephalogram (EEG) recordings (Malhotra & Avidan, 2014; A Rechtschaffen & Kales, 1968). Non-REM sleep can be further separated into four different stages using the traditional terminology and definitions (for updated definitions see manual by the American Academy of Sleep Medicine) (Carskadon & Dement, 2011; Fuller, Gooley, & Saper, 2006; Iber, Ancoli-Israel, Chesson, & Quan, 2007). Stage 1 sleep is a relatively short transitional state between wakefulness and sleep with a very low arousal threshold. Stage 2 sleep is a period of light sleep marked by slowing of brain activity and constitutes the majority of total sleep time. Stages 3 and 4 are known as slow wave sleep (SWS), marked by significantly slowed brain activity, heartbeat, and breathing. During REM sleep, the electrical frequency of brain activity closely resembles that of wakefulness and the eyes move rapidly from side to side, while muscle activity is suppressed. The majority of dreams occur during this stage of sleep, which has been hypothesized to play an important role in pruning and strengthening of neural networks, memory consolidation, learning, recuperative processes, and protoconsciousness (Crick & Mitchison, 1983; Hobson, 2009; J. M. Siegel, 2001; Jerome M. Siegel, 2005). On the other hand, NREM sleep – specifically slow wave sleep – is associated with restorative sleep and hypothesized to serve a number of crucial functions including energy conservation, information processing, synaptic plasticity, and cellular maintenance (Jerome M. Siegel, 2005; Vyazovskiy & Delogu, 2014). In adults, sleep typically follows a predictable pattern, beginning in Stage 1 and progressing through deeper NREM stages before initiating the first episode of REM sleep approximately 80-100 minutes after sleep onset

(Carskadon & Dement, 2011; Gunzelmann et al., 2009). NREM and REM sleep will cycle through this pattern approximately every 90 minutes, with REM sleep periods growing longer across the night. Consequently, the majority of the deep, restorative sleep occurs in the first half of the sleep episode.

The 2-Process Model of sleep regulation predicts that wake behavior is influenced in part by a homeostatic Process S, which builds during wakefulness and dissipates during sleep. As sleep is curtailed or eliminated, the opportunity for Process S to dissipate is shortened and it gradually accumulates over the course of several days (A. A. Borbély, 1982; Alexander A. Borbély, Daan, Wirz-Justice, & Deboer, 2016; Fuller et al., 2006). The putative marker for homeostatic sleep pressure is considered to be the intensification of sleep EEG slow wave activity or slow wave sleep, indicative of increased sleep need (Dijk & Czeisler, 1995). Following a period of sleep loss, reductions in sleep onset latency, as well as rapid eye movement (REM) sleep and slow wave sleep (SWS) latency are observed, consistent with increased sleep drive (Dijk & Czeisler, 1995). Counteracting the sleep drive is Process C, controlled by an internal biological clock known as the circadian pacemaker, residing in the suprachiasmatic nucleus (SCN) of the hypothalamus. Endogenous circadian rhythms are entrained to the Earth's rotation and regulate the timing of sleep and waking, among a host of other biological processes (Dijk & Czeisler, 1995; Fuller et al., 2006). Circadian phase in mammals can be accurately measured via the timing of melatonin secretion from the pineal gland (Cajochen, Krauchi, & Wirz-Justice, 2003). The increase in melatonin during the night is paralleled by a drop in core body temperature, which is often used as a proxy for circadian phase. It is thought that the interaction of these two processes is responsible for the modulation of neurobehavioral functioning during wakefulness following a period of sleep loss (Saper, Fuller, Pedersen, Lu, & Scammell, 2010).

Interindividual differences in sleep architecture are relatively stable across multiple sleep EEG recordings and between monozygotic twins, suggesting there may be phenotypic markers of

sleep (Buckelmüller, Landolt, Stassen, & Achermann, 2006; Linkowski, Kerkhofs, Hauspie, Susanne, & Mendlewicz, 1989; Merica & Gaillard, 1985; Webb & Campbell, 1983). An age-dependent lightening of the homeostatic process has been well-documented, marked by reduced total sleep time, greater nighttime awakenings, and decreased slow wave sleep in older adults (Dorffner, Vittr, & Anderer, 2015; Li, Vitiello, & Gooneratne, 2018; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Additionally, older individuals typically experience a shift in the circadian process to favor earlier bedtimes and rise times, and less tolerance for shifts in circadian phase caused by jet lag (Ancoli-Israel, 2009; Li et al., 2018; Turek, Penev, Zhang, van Reeth, & Zee, 1995; Yoon et al., 2003). There is some evidence for gender differences in sleep PSG, with higher sleep efficiency and faster sleep onset in women as compared with men (Goel, Kim, & Lao, 2005; Tucker, Dinges, & Van Dongen, 2007). Together, age and gender have been shown to account for <30% of interindividual variability in baseline sleep variables (Tucker et al., 2007)

Researchers have suggested that individuals with habitually higher homeostatic sleep pressure are predisposed to greater vulnerability to accumulating deficits during periods of sleep loss. One study of 36 hours of total sleep deprivation found that individuals with the greatest deficits in neurobehavioral performance following sleep loss had higher sleep efficiency (SE) and less wakefulness after sleep onset (WASO) during baseline sleep, as well as more consolidated recovery sleep (Møst, E. I., Baynard, M. D., Fox, C. G., Blaauw, M. S., Ballas, C., Dinges, D. F., & Van Dongen, 2003). The proportion of time spent in Stage 1 sleep during baseline has been negatively associated with PVT lapses and reaction times, showing better PVT performance with increased Stage 1 sleep time (Chua, Yeo, Lee, Tan, Lau, Tan, et al., 2014). In other work, vulnerable and resilient individuals showed similar levels of homeostatic sleep pressure and did not differ in the dissipation of sleep drive across the night during baseline sleep as measured by sleep onset latency, total sleep time, sleep efficiency, WASO, and proportion of time spent in Stage 1, Stage 2, slow wave sleep (SWS), or rapid eye movement (REM) sleep (Chua, Yeo, Lee,

Tan, Lau, Cai, et al., 2014). Researchers noted increased Stage 1 sleep in resilient individuals at baseline (5.3% of total sleep time, as compared with 3.2% for the vulnerable group) as well as slightly shorter sleep duration, but concluded that baseline homeostatic sleep drive does not correlate with waking performance and vulnerability to sleep deprivation given lack of findings on other sleep variables.

Prior research investigating the relationship between habitual sleep timing and duration with interindividual differences in response to sleep loss has yielded mixed findings. Aeschbach et al (2001) were the first to examine the impact of sleep loss on individuals identified as short sleepers (habitual nightly sleep <6h) and long sleepers (habitual nightly sleep >9h) in a constant routine protocol across 40h of wakefulness. Results showed that short sleepers reported lower levels of subjective sleepiness despite evidence for greater homeostatic pressure during extended wakefulness. Authors suggested that individuals who require less sleep might be less vulnerable to the effects of sleep loss on subjective measures. Later studies found no difference in subjective reports of sleepiness, sleep quality, and sleep duration between individuals classified as vulnerable or resilient on PVT or working memory performance decrements across TSD or SR (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014; William D Scott Killgore et al., 2009; Mallis et al., 2001; Mu et al., 2005; Sletten, Segal, Flynn-Evans, Lockley, & Rajaratnam, 2015). One study did not detect a difference between vulnerable and resilient participants on pre-laboratory measures of sleep duration using actigraphy and sleep diaries, but did not investigate patterns of sleep timing and variability in schedules (William D Scott Killgore et al., 2009). Another found a modest positive correlation between average sleep duration as measured by actigraphy prior to laboratory participation and the rate of change in behavioral alertness during chronic partial sleep restriction, with habitually longer sleepers showing greater vulnerability to the effects of sleep loss (Van Dongen, Maislin, Mullington, & Dinges, 2003).

A comparison of individuals who were classified as vulnerable or resilient to two nights of SR to 5h and 3h TIB based on PVT performance decrements showed that vulnerable individuals had a later circadian phase as measured by dim light melatonin onset, despite no significant differences of habitual bedtimes between the two groups (Sletten et al., 2015). One study conducted under strictly controlled laboratory conditions that regulated prior sleep history found no difference in PERCLOS (Percentage of Eye Closure), blink rate, or circadian phase determined by core body temperature between individuals who were later identified as resilient or vulnerable based on decrements in PVT performance during 36-40h TSD (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014). However, a study examining performance across three repeated exposures to TSD found that circadian phase, as determined by core body temperature, accounted for 28% of the variance in performance on a working memory task, despite manipulation of prior sleep history the week before the study protocol (Van Dongen et al., 2004). Confirming previous findings, results showed that subjects with a later circadian phase (“night owls”) had greater decrements in performance during TSD.

Previously, self-reported chronotype (morningness-eveningness) has been shown to discriminate between Types 1 and 2 (resilient and average performers) on PVT performance during total sleep deprivation (Mallis et al., 2001). Additionally, some studies have shown that individuals who are rigid in their circadian rhythm have higher levels of subjective sleepiness and impaired performance on the PVT during total sleep deprivation, as compared with flexible types (Marcoen, Pattyn, Vandekerckhove, & Mairesse, 2014). In one study, individuals classified as resilient to sleep loss had more variability in self-reported sleep-wake schedules as compared with vulnerable participants, who displayed more consistent timing despite a lack of any sleep manipulation in the week prior (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014). Another study found that individuals with greater vulnerability to microsleeps following sleep restriction had more consistent bedtimes, shorter sleep onset latencies, and fewer nighttime awakenings during habitual sleep measured by actigraphy (Innes, Poudel, & Jones, 2013). This may reflect a self-

imposed consistency in an effort to counteract greater vulnerability to negative effects of sleep disturbance. Results from Chapter 1 failed to find a significant association of chronotype as measured by the Morningness-Eveningness Questionnaire (MEQ) (J. A. Horne & Ostberg, 1976a). It is possible that individuals are poor reporters of their chronotype and so the MEQ does not capture true differences in sleep timing preferences.

Given the discrepancy in the findings, further research is needed to elucidate the relationship between baseline homeostatic sleep pressure, habitual sleep duration and timing, and interindividual vulnerability to the neurobehavioral effects of sleep loss. Wrist actigraphy data on habitual bedtimes and wake times in the weeks prior to and following the study protocol provide a unique opportunity to examine habitual sleep duration, sleep timing and variability in the sleep schedule of individuals outside the laboratory. An objective measure of total sleep duration in the week prior to study participation provides an indirect measure of homeostatic sleep pressure, as it would be expected that individuals with greater sleep need strive to obtain more sleep on average outside of the laboratory. Wrist actigraphy also provides objective data on preferred sleep timing by reporting habitual sleep and wake times, and can be used to examine the question of habitual sleep timing as a possible predictor of inter-individual differences in response to sleep loss. As individuals are typically asked to keep to a regular schedule in the week prior to participation in the study protocol, the observed patterns in actigraphy data for this time period may be misleading and not reflective of true habitual sleep schedules. Therefore, it is important to also investigate potential differences in habitual sleep patterns among vulnerability groups outside of the constraints set by the protocol, by also examining actigraphy data for the 7 days following study participation. This serves as an additional source of information on habitual sleep timing, and can examine any possible rebound effects in the timing and duration of sleep following chronic partial sleep restriction in the lab. The present study examines whether vulnerability groups differ in baseline homeostatic sleep pressure and habitual sleep patterns by examining baseline sleep architecture as measured by polysomnography in the laboratory, and sleep timing

and duration outside of the laboratory prior to and following sleep restriction, as obtained by wrist actigraphy monitoring.

Methods

Measures

PSG - Polysomnographic (PSG) recordings were collected throughout the study using Sandman Suzanne portable digital recording system (128-Hz sampling) on B1, B2, SR1, and SR5. The EEG from the C3-A2 derivation was scored by trained technicians using the criteria of Rechtschaffen and Kales (1968). Sleep onset was determined as the observation of ≥ 3 consecutive 30s epochs of Stage 2-4 or REM sleep. For each night of PSG, total sleep time (TST), sleep onset latency (SOL), the number of awakenings (NWAK), proportion of time spent in rapid eye movement (REM) and slow wave sleep (SWS; Stage 3 or Stage 4), the number of stage shifts throughout the night, latency to onset of REM sleep, and the proportion of TST spent in Stage or Stage 2 sleep were extracted. Present analyses used PSG data from the second baseline night (B2) following an adaptation night in the laboratory (B1). Data were available for n=52 Type 1, n=59 Type 2, and n=80 Type 3 individuals (total N=191 sleep-restricted subjects).

Actigraphy – Study participants were monitored with wrist actigraphy during the week prior to (PRE) and following (POST) participation in the laboratory protocol. Data were collected using the Phillips Respironics “Actiwatch Spectrum” with epoch length set to 1 minute. The “Actiware 5” software by Phillips Respironics was used to download the data and extract the variables of interest. Outcome measures include the average bedtime and wake time, total sleep time (TST), and the standard deviation in the timing of sleep onset and awakening, as well as in the average total sleep times across the seven nights of actigraphy monitoring. Data from the week prior to study participation were available for n=93 Type 1, n=89 Type 2, and n=92 Type 3 individuals

(total N=274 sleep-restricted subjects). Following laboratory sleep restriction, actigraphy data were available for n=89 Type 1, n=88 Type 2, and n=89 Type 3 individuals (total N=266 sleep-restricted subjects).

Data Analysis

A one-way multivariate analysis of variance (MANOVA) was run to examine whether baseline sleep architecture differed among vulnerability groups (Type 1, Type 2, Type 3). Several outliers were noted in the data, and univariate normality was not observed for TST, SOL, and NWAK. Analyses were run on non-transformed data and did not exclude any outliers as the MANOVA is fairly robust to violations of these assumptions (Olson, 1979). Four multivariate outliers were observed, as assessed by Mahalanobis distances greater than 27.88 given 9 dependent variables. Two of these outliers were within the Type 3 group, while the remaining two outliers were in the Type 1 and 2 groups. The multivariate outliers were also included in the analysis to retain maximum information. There was no multicollinearity, as assessed by Pearson correlations (all $r < 0.70$). Due to natural changes in sleep architecture, and the association between age and vulnerability to sleep loss as noted in Chapter 1, age was included as a covariate in the analysis.

Two one-way MANOVAs were conducted to examine whether vulnerability groups (Type 1, Type 2, Type 3) differ in habitual sleep patterns in the 7 days prior to entering the laboratory and after completion of the laboratory protocol. For the purposes of these analyses, average bedtimes and wake times were transformed to numeric variables to represent distance from midnight in hours, with negative values indicating times prior to midnight (i.e. -0.5 indicates 30 minutes prior to midnight or 2330h). Only one extreme outlier was noted in the data for a Type 2 individual on the standard deviation in TST. The outlier was not removed for the analysis, as it contains valuable information regarding variability in sleep schedules. Average TST, sleep and wake times were normally distributed for each group, as assessed by Shapiro-Wilk's test ($p > .05$). Measures of

standard deviation in those three variables were slightly skewed to the right, but were not concerning for the present analyses after review of the Q-Q Normality Plots. No transformations were applied to the data to retain maximum information. There was no multicollinearity among dependent variables, as assessed by Pearson correlation (all absolute $r < 0.80$). One multivariate outlier was observed in the PRE data, and seven multivariate outliers were observed in the POST data, as assessed by a Mahalanobis distance greater than 22.46 given 6 dependent variables. All were kept in the analyses given the large sample size and to retain maximum information. Homogeneity of variance-covariance matrices was not met, as assessed by Box's test of equality of covariance matrices ($p < 0.001$). However, given the roughly equal sample sizes, this was not of significant concern. There was homogeneity of variances, as assessed by Levene's Test of Homogeneity of Variance ($p > .05$). As the data were pooled from three different studies a categorical variable ("Study"), indicating which of the studies contributed the data, was used as a covariate in the model to control for differences in the recovery protocol following chronic partial sleep restriction. Age was also included in the model as a covariate due to indication that it may be associated with vulnerability to the effects of sleep loss, as reported in Chapter 1. If any of the omnibus tests of group differences were statistically significant, post-hoc analyses were conducted to examine pairwise differences between vulnerability groups on each variable of interest. All statistical analyses were conducted in SPSS Version 24.0 (IBM Corp., 2016).

Results

Baseline sleep architecture

On average, the present sample was asleep for 513 ± 55 minutes (mean $\pm$ standard deviation) on the baseline night in the laboratory out of the total 600 minutes time in bed opportunity, with an average sleep onset latency of 19 ± 20 minutes. Participants had 16 ± 12 measured awakenings

throughout the night and 172 ± 49 stage shifts. They spent 9 ± 5 percent of the total sleep time in Stage 1 sleep, 53 ± 8 percent in Stage 2 sleep, 13 ± 7 percent in slow wave sleep, and 24 ± 5 percent in REM sleep, with 72 ± 35 minutes until onset of the first REM episode. Descriptive statistics for all polysomnographic measures for each vulnerability group are displayed in Table 7. Results indicated age had a significant effect on baseline PSG measures, $F(9,179)=5.9$, $p<0.001$. Older individuals had shorter TST, more awakenings, spent a smaller proportion of TST in SWS and a larger proportion of TST in REM. The difference between vulnerability groups on the combined dependent variables was not statistically significant after adjusting for age, $F(18, 360) = 0.94$, $p = 0.53$; Pillai's $V = 0.09$; partial $\eta^2 = .045$.

[Table 7 here]

Habitual Sleep Patterns Outside the Laboratory

Descriptive statistics for all of the actigraphy measures for each vulnerability group in the week prior to and following study participation are displayed in Table 8. During the week prior to laboratory sleep restriction, the present sample slept on average 8 ± 0.6 hours, with a bedtime of $23:50 \pm 54$ minutes and wake time of $07:52 \pm 53$ minutes. Across the 7 days prior to the study, participants had a standard deviation of 38 minutes in their bedtimes, 43 minutes in their wake times, and 49 minutes in total sleep time. Results of the MANOVA found no effect of "Study" on pre-laboratory habitual sleep, $F(6, 264) = 0.998$, $p = 0.43$; Pillai's $V = 0.02$; partial $\eta^2 = .022$. Age was found to have a significant effect on habitual sleep, $F(6, 264)=5.6$, $p<0.001$; Pillai's $V = 0.11$; partial $\eta^2 = .11$, specifically on the average bedtime and wake time (both $p<0.001$), with older adults going to bed and waking up earlier. The difference between vulnerability groups on the combined actigraphy measures in the week prior to study participation was not statistically significant, $F(12, 530) = 0.76$, $p = 0.70$; Pillai's $V = 0.03$; partial $\eta^2 = .017$.

[Tables 8 and 9 here]

In the week following laboratory sleep restriction, the present sample slept on average 7.9 ± 1 hours, with a bedtime of $00:20 \pm 1.2$ hours and wake time of $08:16 \pm 1.3$ hours. Across the 7 days following the study, participants had a standard deviation of 61 minutes in their bedtimes, 73 minutes in their wake times, and 1.4 hours in total sleep time. Descriptive statistics for all of the actigraphy measures for each study protocol in the week prior to and following participation are displayed in Table 9. Completion of a specific laboratory protocol ("Study"), had a significant effect on post-participation habitual sleep, $F(6, 256)=4.4$, $p<0.001$; Pillai's $V = 0.09$; partial $\eta^2=0.09$. Exploratory univariate tests looking at post-laboratory sleep patterns across protocols ("Study"), with age and vulnerability group as covariates, found significant differences in average total sleep time ($p=0.02$), and variability in total sleep time ($p<0.001$), bedtime ($p=0.013$), and wake time ($p<0.001$). Only differences in the variability in TST and wake times remained significant after Bonferroni correction for multiple comparisons (adjusted $p=0.008$). Participants who completed Study 3 had less variability in their wake times (56 ± 5 minutes) and total sleep time (1.1 ± 0.1 hours), as compared with those who completed Study 1 (82 ± 3 minutes standard deviation in wake time; 1.5 ± 0.1 hours standard deviation in TST) and Study 2 (75 ± 5 minutes standard deviation in wake time; 1.5 ± 0.1 hours standard deviation in TST). As with pre-laboratory habitual sleep, age was found to have a significant effect on habitual sleep, $F(6, 256)=3.95$, $p=0.001$; Pillai's $V = 0.09$; partial $\eta^2 = .09$, specifically on the average bedtime and wake time (both $p<0.001$), with older adults going to bed and waking up earlier. There was no statistically significant difference in actigraphy sleep patterns between vulnerability groups following laboratory chronic partial sleep restriction, $F(12, 514)=1.0$, $p=0.44$; Pillai's $V = 0.05$; partial $\eta^2 = .02$.

Discussion

The goal of this study was to examine whether individuals classified as resilient, average, or vulnerable to sleep loss differ in baseline homeostatic sleep pressure and habitual sleep patterns by examining baseline sleep architecture, along with sleep timing and duration outside of the laboratory prior to and following sleep restriction. The present sample replicated prior findings on alterations in sleep architecture with age, despite the fact that all of the participants were younger than 55. In the present sample, older age was associated with shorter total sleep time, more awakenings, smaller proportion of total sleep time spent in slow wave sleep, and a larger proportion of total sleep time spent in REM sleep at baseline. Similarly, older age was associated with earlier habitual bedtimes and wake times both before and after participation in the laboratory protocol. These findings underscore the importance of adjusting for age when examining the impact of sleep loss on sleep architecture and timing. There was no significant difference among vulnerability groups on any of the baseline sleep architecture variables as measured by polysomnography. Similarly, groups did not differ in their habitual sleep outside of the laboratory, as measured by wrist actigraphy prior to and following participation in the study protocol. These findings suggest that observed vulnerability to the effects of sleep loss cannot be attributed to baseline differences in sleep pressure. As the present study relied on sleep architecture variables measured with polysomnography to define homeostatic sleep drive, it does not rule out the possibility that interindividual differences in homeostatic sleep drive between vulnerability groups may be observed in power spectral analysis during sleep or wakefulness.

Lastly, the present study found differences in post-laboratory sleep patterns as measured by actigraphy among participants completing different laboratory protocols. While it is an incidental finding, it is certainly one that is noteworthy. The data used for the analyses were pooled from three chronic partial sleep restriction protocols under the same controlled conditions that required between 11-19 days in the laboratory. To answer the current research questions, data were used only from the first portion of each protocol, which captured two baseline nights in the laboratory followed by five nights of chronic partial sleep restriction to four hours time in bed. The three

protocols differed by the amount of recovery sleep opportunity afforded to the participants at the conclusion of each study. In the case of two protocols, participants also completed a second dose of chronic sleep restriction immediately after a recovery sleep opportunity of varying duration. Data on habitual sleep patterns measured by wrist actigraphy suggest that while individuals do not differ in sleep timing and duration prior to entering the laboratory, they show significant differences in variability of total sleep duration and morning wake times depending on which protocol they completed. Individuals who completed the Study 3 protocol demonstrated reduced variability in total sleep time and wake time as compared with participants who completed either of the other two studies. This particular protocol required a laboratory stay of 15-19 consecutive nights, as compared to 11 and 16 nights required by the other two protocols. Furthermore, it allowed for a single night of recovery sleep opportunity of at least 10h time in bed while the other two protocols included two nights of recovery sleep prior to leaving the laboratory. It appears that participants who remained under controlled laboratory conditions the longest had more consistent wake times, with a standard deviation in their morning wake time of 56 minutes on average, as compared with participants who completed either of the two shorter protocols, who showed average standard deviations in their wake times of 82 and 75 minutes. Additionally, these individuals had less variability in their total sleep time (66 minutes) in the week following their participation in the protocol, compared with participants in the either two protocols who had a standard deviation of 90 minutes in their total sleep times after departing the laboratory. This suggests that long-duration laboratory protocols may have observable effects on sleep patterns of participants even after they depart the laboratory. The present findings are likely due to participant adaptation to a rigid sleep schedule imposed by strict laboratory conditions, which resulted in more consistent sleep patterns for a period of time after completion of the protocol. Alternatively, structured habitual sleep patterns may indicate a self-imposed mechanism for coping with lingering homeostatic sleep debt, as participants in the longest study received only one night of recovery sleep opportunity prior to leaving the laboratory. Studies have reported that individuals who are vulnerable to performance decline on the PVT during sleep loss tend to be

more rigid in their circadian rhythm and have less variability in self-reported sleep-wake schedules (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014; Innes et al., 2013; Marcoen et al., 2014). The implication that laboratory manipulation of sleep, particularly prolonged protocols of significant sleep loss, have a lasting impact on habitual sleep patterns of voluntary participants warrants further study. The assumption that one or two nights of recovery sleep opportunity prior to departing the laboratory is enough to erase any sleep debt accumulated across the protocol is not guaranteed.

Presently, few if any protocols continue to follow participants after the study is completed. Research thus far has focused on neurobehavioral recovery following sleep loss, particularly the temporal dynamics and differential responses of subjective and cognitive performance measures to varying lengths of recovery sleep opportunity (Banks, Van Dongen, Maislin, & Dinges, 2010; Cohen et al., 2010; Ikegami et al., 2009; Lamond et al., 2007). There is no evidence to support the assumption that ten or twelve hours of sleep at the conclusion of a protocol featuring chronic sleep restriction or total sleep deprivation is sufficient to return sleep to baseline in our participants, even if neurobehavioral performance appears to stabilize. These findings suggest that investigators should consider the long term impact of their methods not only on subjective sleepiness and psychomotor alertness, but also on habitual sleep patterns and circadian rhythms of the participants.

Table 7. Polysomnographic measures during baseline sleep (B2) by vulnerability group.

	Group	Mean	Std. Dev.	N
TST (min) ^a	Type 1	504.53	45.67	52
	Type 2	517.24	56.79	59
	Type 3	516.53	58.67	80
SOL (min) ^b	Type 1	18.48	21.43	52
	Type 2	22.46	25.37	59
	Type 3	16.51	15.10	80
NWAK ^c	Type 1	17.15	12.19	52
	Type 2	14.22	10.46	59
	Type 3	17.34	12.28	80
% SWS ^d	Type 1	12.93	7.47	52
	Type 2	13.41	7.03	59
	Type 3	13.34	7.58	80
% REM ^e	Type 1	23.75	3.71	52
	Type 2	23.80	5.29	59
	Type 3	24.12	6.22	80
Stage Shifts ^f	Type 1	176.35	46.17	52
	Type 2	171.07	48.12	59
	Type 3	170.85	52.72	80
REM Latency (min) ^g	Type 1	74.06	32.29	52
	Type 2	71.89	34.71	59
	Type 3	71.87	36.29	80
% Stage 1 ^h	Type 1	9.59	6.00	52
	Type 2	9.63	5.50	59
	Type 3	8.88	4.73	80
% Stage 2 ⁱ	Type 1	53.44	8.37	52
	Type 2	53.15	8.11	59
	Type 3	53.59	8.07	80

^aTotal sleep time in minutes^bSleep onset latency in minutes^cNumber of awakenings after sleep onset^dProportion of total sleep time spent in slow wave sleep^eProportion of total sleep time spent in REM sleep^fNumber of stage shifts throughout the night^gREM sleep onset latency in minutes^hProportion of total sleep time spent in Stage 1 sleepⁱProportion of total sleep time spent in Stage 2 sleep

Table 8. Actigraphy measures prior to (PRE) and following (POST) laboratory participation by vulnerability group.

			PRE		POST	
			Mean	Std. Dev.	Mean	Std. Dev.
Vulnerability	Type 1	Bedtime ^a	-0.31	0.86	0.06	1.08
		Wake Time ^b	7.78	0.91	8.02	1.40
		TST ^c	8.08	0.62	7.90	0.91
		Bedtime Variability ^d	35.41	20.52	63.95	53.79
		Wake Time Variability ^e	41.41	23.37	67.68	36.70
		TST Variability ^f	0.78	0.41	1.35	0.69
	Type 2	Bedtime ^a	-0.16	0.90	0.45	1.20
		Wake Time ^b	7.90	0.91	8.40	1.12
		TST ^c	8.06	0.69	7.92	1.02
		Bedtime Variability ^d	37.82	24.40	59.26	36.61
		Wake Time Variability ^e	42.32	19.41	73.68	40.39
		TST Variability ^f	0.81	0.45	1.45	0.74
	Type 3	Bedtime ^a	-0.01	0.92	0.49	1.41
		Wake Time ^b	7.94	0.84	8.38	1.39
		TST ^c	7.96	0.56	7.86	0.99
		Bedtime Variability ^d	41.36	21.53	61.04	35.67
		Wake Time Variability ^e	46.54	24.65	77.81	43.38
		TST Variability ^f	0.88	0.47	1.43	0.79

^aAverage bedtime in hours from midnight

^bAverage wake time in hours from midnight

^cTotal sleep time (TST) in hours

^dStandard deviation of bedtimes across 7 days in minutes

^eStandard deviation of wake times across 7 days in minutes

^fStandard deviation in total sleep time across 7 days in hours

Table 9. Actigraphy measures prior to (PRE) and following (POST) laboratory participation by Study.

		PRE		POST	
		Mean	Std. Dev.	Mean	Std. Dev.
Study 1	Bedtime ^a	-0.16	0.93	0.34	1.20
	Wake Time ^b	7.93	0.93	8.47	1.42
	TST ^c	8.09	0.64	8.05	0.99
	Bedtime Variability ^d	38.55	20.60	67.53	50.75
	Wake Time Variability ^e	43.22	21.36	81.82	43.57
	TST Variability ^f	0.86	0.43	1.54	0.76
Study 2	Bedtime ^a	0.12	0.85	0.64	1.61
	Wake Time ^b	8.01	0.85	8.36	1.31
	TST ^c	7.88	0.69	7.67	1.11
	Bedtime Variability ^d	42.97	25.44	62.09	33.56
	Wake Time Variability ^e	49.69	25.19	75.05	36.36
	TST Variability ^f	0.86	0.49	1.52	0.70
Study 3	Bedtime ^a	-0.41	0.81	0.04	0.89
	Wake Time ^b	7.65	0.80	7.82	0.97
	TST ^c	8.06	0.52	7.78	0.74
	Bedtime Variability ^d	33.37	21.68	49.26	28.53
	Wake Time Variability ^e	38.44	21.79	54.70	30.18
	TST Variability ^f	0.72	0.42	1.08	0.62

^aAverage bedtime in hours from midnight

^bAverage wake time in hours from midnight

^cTotal sleep time (TST) in hours

^dStandard deviation of bedtimes across 7 days in minutes

^eStandard deviation of wake times across 7 days in minutes

^fStandard deviation in total sleep time across 7 days in hours

CHAPTER 5: HOMEOSTATIC RESPONSE TO CHRONIC PARTIAL SLEEP RESTRICTION AND INTERINDIVIDUAL VULNERABILITY TO SLEEP LOSS

Introduction

The 2-Process Model of sleep regulation predicts that wake behavior is influenced in part by a homeostatic Process S, which builds during wakefulness and dissipates during sleep. As sleep is curtailed or eliminated, the opportunity for Process S to dissipate is shortened and it gradually accumulates over the course of several days (A. A Borbély, 1982). This sleep drive is counterbalanced by Process C, which is controlled by an internal biological clock, known as the circadian pacemaker, residing in the suprachiasmatic nucleus (SCN). It is thought that the interaction of the two processes, S and C, is responsible for the modulation of neurobehavioral functioning during wakefulness following a period of sleep loss. The putative marker for homeostatic sleep pressure is considered to be the intensification of sleep EEG slow wave activity or slow wave sleep (SWS), indicative of increased sleep need (Dijk & Czeisler, 1995). It has been proposed as being critical to the recovery of waking neurobehavioral functions (A A Borbély & Achermann, 1999; J. Horne, 1988).

Much of the work on homeostatic response to sleep loss examines sleep architecture during extended recovery sleep opportunity following sleep deprivation or chronic partial sleep restriction. Both protocols elicit an increase in total sleep time, rapid eye movement (REM) sleep, and SWS relative to baseline, reflecting increased homeostatic sleep pressure (Banks, Dongen, et al., 2010; Tucker et al., 2007). During protocols of chronic partial sleep restriction, observed changes in sleep architecture include reductions in sleep onset latency, Stage 2 sleep and REM sleep (Banks, Dongen, et al., 2010). No significant change in the absolute amount of time spent in slow wave sleep was found, but given the significant reduction of sleep opportunity within the protocol, the proportion of time spent in SWS increased accordingly. An elegant study of sleep restriction and augmentation demonstrated dose-dependent changes in total sleep time and

sleep stages with increasing time in bed (TIB) (Belenky et al., 2003). During sleep restriction to 3 and 5 hours time in bed, individuals had reductions in Stages 1, 2, and REM sleep. During sleep augmentation to 9 hours time in bed, individuals saw an increase in Stage 1 and REM sleep time. Again, total time spent in SWS did not vary with TIB.

Data from a study of repeated exposure to total sleep deprivation provided the first evidence of moderate stability of interindividual differences in the buildup and dissipation of the homeostatic sleep drive (Rusterholz, Tarokh, Van Dongen, & Achermann, 2017). Authors reported intraclass correlation coefficients of 0.56 and 0.48 for the accumulation and reduction of homeostatic sleep pressure, respectively. Furthermore, the findings indicated that these two parameters of Process S were not interdependent and likely reflected two distinct phenotypic traits. Other research has found differences in the rate of dissipation of homeostatic sleep pressure between individuals who self-identified as morning or evening types, as well as among groups with different genetic polymorphisms of the PER3 and ADA genes (Bachmann et al., 2012; C. Schmidt et al., 2009; Viola et al., 2007).

It has been suggested that individuals vulnerable to the effects of sleep loss experience greater buildup of homeostatic sleep pressure, which results in worse performance under conditions of sleep loss. In contrast, resilient individuals are thought to not experience the same increase in homeostatic sleep pressure with extended time spent awake, and thus not suffer from the same level of impairment as individuals with a more sensitive homeostatic process. Individuals who showed the greatest deficits during two sessions of 36h total sleep deprivation had more consolidated recovery sleep following sleep loss, suggesting increased buildup of the homeostatic sleep drive (Møst, E. I., Baynard, M. D., Fox, C. G., Blaauw, M. S., Ballas, C., Dinges, D. F., & Van Dongen, 2003). Researchers put forth that some individuals have a higher sleep need associated with greater vulnerability to the effects of sleep loss. A later study found no difference between vulnerable and resilient individuals on sleep onset latency (SOL), TST, SE,

WASO, Stage 1 and 2, SWS, or REM during recovery sleep (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014). When considering changes in sleep architecture or physiology as a result of sleep loss, no differences have been observed between vulnerable and resilient individuals, as categorized by performance decrements on the PVT across TSD or SR, in the buildup or dissipation of homeostatic sleep pressure in response to sleep loss (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014).

The present study examines the effect of interindividual vulnerability to sleep loss on homeostatic response to five consecutive nights of sleep restriction to four hours time in bed (TIB). In contrast with prior work, the current analysis relies on a much larger sample of individuals who completed a strict laboratory protocol including polysomnography (PSG) recordings at baseline and following sleep restriction. It explores potential differences in homeostatic response to chronic partial sleep restriction among individuals characterized as vulnerable, average, or resilient to the effects of sleep loss, in addition to overall group differences between sleep restricted and control participants.

Methods

Measures

Sleep Physiology

Polysomnographic (PSG) recordings were collected throughout the study using Sandman Suzanne portable digital recording system (128-Hz sampling) on B1, B2, SR1, and SR5. The EEG from the C3-A2 derivation was scored by trained technicians using the criteria of Rechtschaffen and Kales (1968). Sleep onset was determined as the observation of ≥ 3 consecutive 30s epochs of Stage 2-4 or rapid eye movement (REM) sleep. Primary outcome variables for this study were the total sleep time (TST), sleep onset latency (SOL), number of

awakenings (NWAK), the proportion of TST spent in slow wave sleep (SWS; Stage 3 or Stage 4 sleep), and the proportion of TST spent in rapid eye movement (REM) sleep. Subjects missing PSG data on B2 (due to technical problems) were excluded from all sleep physiology analyses. Complete PSG data at baseline were available for N=208 participants.

Data Analysis

Mixed-effects models were used to examine whether change in sleep architecture variables differed between participants in the Control and Sleep Restriction conditions, as well as among vulnerability groups (Type 1, Type 2, Type 3) over several days of sleep restriction (B2, SR1, SR5). Analyses were repeated with age added as a covariate in each model to account for natural changes in sleep architecture with age and prior findings suggesting older individuals are less impacted by sleep loss as compared with younger participants, as discussed in Chapters 1 and 2 (Adam et al., 2006; Ancoli-Israel, 2009; Bliese et al., 2006; Landolt et al., 2012; Li et al., 2018; Turek et al., 1995; Yoon et al., 2003). Maximum likelihood estimation was used to address missing data in each of the models. Bonferroni adjusted p-values were used to account for multiple comparisons in any post-hoc analyses following a significant omnibus test (Dunn, 1961). Statistical analyses were conducted in SPSS (Version 24.0; IBM Corp., 2016).

Results

The present sample ranged in age from 22-45. There was no difference in age between Control (Mean=29.8, SD=6.9) and Sleep Restricted participants (Mean=29.9, SD=6.9). Of the Control participants, 53% self-identified as female, compared with 48% of the Sleep Restricted group. Change in polysomnographic measures across days in the protocol for the control and sleep restricted subjects can be seen in Figure 2 and Table 10.

[Figure 2 & Table 10 here]

Participants in the control group showed a decrease in total sleep time from 523.2 ± 75.4 minutes at baseline (B2) to 477.1 ± 58.3 minutes on the fifth night of sleep restriction (SR5) (*Figure 2A*). Sleep onset latency increased from 13.2 ± 11.1 minutes to 33.7 ± 33.5 minutes, and the number of awakenings increased from 9 ± 5 to 11 ± 7 (*Figures 2B-C*). The proportion of TST spent in SWS and REM sleep did not change across protocol days (*Figure 2D-E*). The observed changes are likely driven by the dissipation of remaining sleep debt and saturation of the homeostatic sleep drive, as individuals were required to remain in bed for 10 hours on each night spent in the laboratory.

Participants undergoing sleep restriction showed a decline in TST from 513.5 ± 54.8 minutes at baseline to 231.2 ± 11.2 minutes at SR5 (*Figure 2A*), as would be expected given the decrease in sleep opportunity from 10 hours to 4 hours time in bed. Sleep onset latency shrunk from 18.9 ± 20.5 minutes to 2.1 ± 3.1 minutes, and the number of awakenings fell from 16 ± 12 to 3 ± 3 , indicative of increased sleep pressure in response to chronic partial sleep restriction (*Figure 2B-C*). Sleep restricted participants also showed a large increase in the proportion of TST spent in slow wave sleep (SWS), from $13.3 \pm 7.4\%$ at baseline to $28.2 \pm 13.3\%$ on the fifth night of sleep restriction (*Figure 2D*). There was no significant change in the proportion of TST spent in REM sleep (*Figure 2E*).

[Figure 3 & Table 11 here]

Change in polysomnographic measures across days in the protocol for all sleep restricted subjects grouped by vulnerability can be seen in Figure 3 and Table 11. The three different vulnerability groups (Type 1, Type 2, Type 3) did not differ in their response to sleep restriction as measured by TST, SOL, NWAK, SWS, and REM (all $p > 0.05$).

There was a significant effect of protocol day ($F(2, 196.8)=2834.1, p<0.001$) on TST (*Figure 3A*). There was no significant effect of vulnerability group ($F(2,197.7)=0.94, p=0.39$) or interaction effect ($F(4,196.8)=0.59, p=0.673$) on TST. Following the significant decrease in TST between baseline and during sleep restriction, participants obtained significantly more sleep on the fifth night of sleep restriction (SR5) as compared with the first night of sleep restriction (SR1) ($p<0.001$), suggesting increased sleep pressure over time. Including age as a covariate in the model reduced overall model fit as indicated by a small decrease in -2 Log Likelihood from 5022.5 to 5017.2 but an increase in Bayesian information criterion (BIC) values from 5117.9 to 5150.7 (Burnham & Anderson, 2004). There was a significant effect of age on TST ($F(1, 226.7)=20.9, p<0.001$) and an interaction between age and protocol day ($F(2, 274.2)=3.8, p<0.023$), with shorter TST associated with older age, but the interaction did not meet statistical significance after adjustment for multiple comparisons. There was no significant interaction between protocol day, age, and vulnerability ($p=0.49$).

The main effect of protocol day was significant for sleep onset latency (SOL; $F(2, 195.6)=71.8, p<0.001$) (*Figure 3B*). Compared with baseline, SOL was 12.5 minutes shorter on SR1 ($p<0.001$), and 14.5 minutes shorter on SR5 ($p<0.001$). There was no significant effect of vulnerability group ($F(2,195.2)=0.81, p=0.45$) or interaction effect ($F(4,195.6)=0.95, p=0.43$). Including age as a covariate in the model reduced overall model fit as indicated by increases in -2 Log Likelihood and BIC values from 3783.7 to 3799.0 and from 3879.02 to 3932.4, respectively (Burnham & Anderson, 2004). There was a significant effect of age on SOL ($F(1, 219.8)=3.9, p=0.049$), but this did not reach statistical significance after adjusting for multiple comparisons. There was no significant interaction between protocol day and age, or protocol day, age, and vulnerability (both $p>0.10$).

There was a significant effect of protocol day on the number of awakenings (NWAK; $F(2, 194.9)=163.6, p<0.001$) (*Figure 3C*). Compared with baseline, there were 12 fewer awakenings on SR1 ($p<0.001$) and 14 fewer awakenings on SR5 ($p<0.001$). There was no significant effect of vulnerability group ($F(2,200.0)=2.5, p=0.08$) or interaction between the two ($F(4,194.9)=0.89, p=0.47$). Including age as a covariate in the model reduced overall model fit as indicated by increases in -2 Log Likelihood and BIC values from 3333.7 to 3429.1 and from 3429.01 to 3562.6, respectively (Burnham & Anderson, 2004). There was a significant effect of age on the number of awakenings ($F(1, 252.5)=31.7, p<0.001$), with older age associated with more awakenings. The interaction between age and protocol day did not meet statistical significance after adjusting for multiple comparisons ($F(2, 276.6)=4.4, p=0.013$). There was no significant interaction between protocol day, age, and vulnerability ($p=0.33$).

There was a significant effect of protocol day on the proportion of time spent in slow wave sleep (SWS; $F(2, 192.1)=315.5, p<0.001$) (*Figure 3D*). Compared with baseline, participants spent 13% more time in SWS on SR1 ($p<0.001$) and 14% more time in SWS on SR5 ($p<0.001$). There was no significant effect of vulnerability group ($F(2,201.2)=0.27, p=0.76$) or interaction between vulnerability group and protocol day ($F(4,192.2)=0.93, p=0.45$). Including age as a covariate in the model reduced overall model fit as indicated by increases in -2 Log Likelihood and BIC values from 3956.6 to 4304.1 and from 4051.9 to 4437.6, respectively (Burnham & Anderson, 2004). There was a significant effect of age on the proportion of time spent in SWS, with older participants spending less time in SWS ($F(1, 496.3)=80.7, p<0.001$). There was also a significant interaction between age and protocol day on proportion of time spent in SWS, such that the association between age and SWS diminished with increasing time in the protocol ($F(2, 372.3)=6.7, p=0.001$). There was no significant interaction between protocol day, age, and vulnerability group on proportion of time spent in SWS ($p=0.51$).

There was a significant effect of protocol day on the proportion of time spent in REM sleep ($F(2, 195.8)=9.7, p<0.001$) (*Figure 3E*). Compared with baseline, participants spent 2% less time in REM on SR1 ($p=0.045$) and 2.7% more time in REM on SR5 ($p=0.001$). There was no significant effect of vulnerability group ($F(2,203.4)=0.61, p=0.55$) or interaction between the two ($F(4,202.3)=1.7, p=0.15$). Including age as a covariate in the model reduced overall model fit as indicated by increases in -2 Log Likelihood and BIC values from 3749.2 to 3809.3 and from 3844.5 to 3942.7, respectively (Burnham & Anderson, 2004). There was a significant effect of age on the proportion of total sleep time spent in REM sleep, with more REM sleep in older individuals ($F(1, 530.2)=23.3, p<0.001$). There was no significant interaction between age and protocol day ($p=0.40$) or between protocol day, age, and vulnerability ($p=0.41$) on the proportion of TST spent in REM sleep.

Discussion

This study examined the effect of interindividual vulnerability to sleep loss on homeostatic response to five consecutive nights of sleep restriction to four hours time in bed (TIB). The present data replicate prior findings on the effect of sleep loss and show increased homeostatic sleep pressure, measured by faster sleep onset latencies, fewer nighttime awakenings, and increased proportion of total sleep time spent in slow wave sleep, in individuals who completed the sleep restriction protocol. Results indicate that individuals who differ in vulnerability to the neurobehavioral effects of sleep loss do not differ in the rate of accumulation of homeostatic sleep pressure during chronic partial sleep restriction. All sleep-restricted subjects, regardless of their vulnerability type as classified by change in performance on the PVT from baseline, showed increased sleep pressure on the first and fifth nights of sleep restriction as compared with baseline sleep.

Older age was associated with reduced total sleep time, more frequent awakenings during the night, a smaller share of total sleep time spent in slow wave sleep, and increased time spent in REM sleep, in line with prior research. However, in each of the five models the overall fit was reduced with the addition of age as a covariate. No significant interactions were observed between age, time in the protocol, and vulnerability group on any of the sleep variables. While sleep architecture changes with age, this does not appear to impact the relationship between vulnerability to the effects of sleep loss, sleep restriction, and homeostatic response to sleep loss.

This is the largest study to date to target this question, with a sample size of more than two hundred healthy adults who completed the same protocol for chronic partial sleep restriction under controlled laboratory conditions. Previous studies on this topic have yielded mixed results, including one study of sleep architecture differences during extended sleep opportunity following total sleep deprivation that found no difference between individuals identified as vulnerable and resilient based on change in PVT performance in response to sleep loss (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014; Møst, E. I., Baynard, M. D., Fox, C. G., Blaauw, M. S., Ballas, C., Dinges, D. F., & Van Dongen, 2003). The present results refute the hypothesis that individuals resilient to the effects of sleep loss do not accumulate sleep deficits to the same degree as those who are vulnerable.

A limitation of the study is the focus on sleep architecture to the exclusion of power spectral activity (PSA) during sleep across days in the protocol. The putative marker for homeostatic sleep pressure is considered to be the intensification of sleep EEG slow wave activity or delta frequency, which has been observed following TSD as well as SR (Achermann & Borbély, 1998; Dijk & Czeisler, 1995). Baseline comparison of power spectral data between individuals identified as vulnerable or resilient to 26-40h total sleep deprivation on the basis of PVT performance decline found that vulnerable subjects had more spectral power in the theta range of the waking EEG at baseline, suggesting higher homeostatic sleep pressure at rested wakefulness (Chua,

Yeo, Lee, Tan, Lau, Cai, et al., 2014). During extended wakefulness, vulnerable individuals show higher theta activity and more delta power as compared with resilient subjects after habitual bedtime. Similarly, individuals with higher spectral power in the very-low frequency band at baseline later showed greater increases in PVT lapses following TSD. These findings suggest that resilient individuals are in a constant state of higher arousal, as measured by sympathetic activity, reduced sleep time and sleep efficiency, as well as lower theta activity during wake. However, when considering changes in sleep physiology as a result of sleep loss, no difference has been observed between vulnerable and resilient individuals, as categorized by performance decrements on the PVT across total sleep deprivation or sleep restriction, in the buildup or dissipation of homeostatic sleep pressure in response to sleep loss (Chua, Yeo, Lee, Tan, Lau, Cai, et al., 2014; O Tkachenko, Abe, Basner, & Dinges, 2016). Data on power spectral activity were collected as part of all study protocols that were used to compile the present dataset. Future work can re-examine whether baseline levels of spectral power or changes in power spectral activity in response to chronic partial sleep restriction differ between individuals who are vulnerable and resilient to the neurobehavioral effects of sleep loss using this much larger sample size.

Present findings offer overwhelming evidence that individuals who are identified as vulnerable or resilient to the effects of sleep loss on the basis of PVT performance decline do not differ in the accumulation of sleep pressure as measured by changes in sleep architecture under sleep restriction. This suggests the possibility of interindividual differences not in the accumulation of sleep debt, but rather in a distinct process which promotes wakefulness in the presence of growing sleep pressure.

Table 10. Sleep polysomnography measures for Control and Sleep Restricted participants at baseline (B2) and following one (SR1) and five (SR5) nights of sleep restriction to 4h time in bed opportunity.

		Control		Sleep Restricted	
		Mean	Std. Dev.	Mean	Std. Dev.
B2	TST ^a	523.2	75.4	513	54.8
	SOL ^b	13.2	11.1	18.9	20.5
	NWAK ^c	9	5	16	12
	% SWS ^d	11.9	6.6	13.3	7.4
	% REM ^e	22.4	3.5	23.9	5.3
SR1	TST ^a	501.4	45.3	223.2	12.2
	SOL ^b	20.5	18.7	4	4.7
	NWAK ^c	11	6	5	4
	% SWS ^d	12.3	6.9	26.6	13.3
	% REM ^e	21.6	5.2	22.8	7.6
SR5	TST ^a	477.1	58.3	231.2	11.2
	SOL ^b	33.7	33.5	2.1	3.1
	NWAK ^c	11	7	3	3
	% SWS ^d	12.8	6.8	28.2	13.3
	% REM ^e	22.3	4.8	25.6	7.9

^aTotal sleep time (TST) in minutes

^bSleep onset latency in minutes

^cNumber of awakenings after sleep onset

^dProportion of TST spent in slow wave sleep

^eProportion of TST spent in REM sleep

Table 11. Sleep polysomnography measures at baseline (B2) and following one (SR1) and five (SR5) nights of sleep restriction to 4h time in bed opportunity by vulnerability group.

		Type 1		Type 2		Type 3		Control	
		Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.	Mean	Std.Dev.
B2	TST ^a	504.5	45.7	517.2	56.8	516.5	58.7	523.2	75.4
	SOL ^b	18.5	21.4	22.5	25.4	16.5	15.1	13.2	11.1
	NWAK ^c	17	12	14	10	17	12	9	5
	% SWS ^d	12.9	7.5	13.4	7	13.3	7.6	11.9	6.6
	% REM ^e	23.7	3.7	23.8	5.3	24.1	6.2	22.4	3.5
SR1	TST ^a	222.9	10.4	223.9	14.9	223	11.4	501.4	45.3
	SOL ^b	4.2	4.5	3.8	4.6	4.1	4.9	20.5	18.7
	NWAK ^c	5	4	4	3	5	4	11	6
	% SWS ^d	26.5	13.2	27	13.7	26.4	13.3	12.2	6.9
	% REM ^e	22.2	7.2	23.7	8.7	22.6	6.9	21.6	5.2
SR5	TST ^a	231.2	8.6	231.8	15.6	230.8	8.7	477.1	58.3
	SOL ^b	2.5	3.3	1.7	3	2.1	3	33.7	33.5
	NWAK ^c	3	3	2	2	3	3	11	7
	% SWS ^d	27.7	14.8	29.6	12.8	27.4	12.7	12.8	6.8
	% REM ^e	24.4	7.3	25.1	7.4	26.9	8.6	22.3	4.8

^aTotal sleep time (TST) in minutes

^bSleep onset latency in minutes

^cNumber of awakenings after sleep onset

^dProportion of TST spent in slow wave sleep

^eProportion of TST spent in REM sleep

Figure 2. Change in polysomnographic sleep measures across days in the study protocol (B2 – Baseline; SR1 – 1st night of sleep restriction; SR5 – 5th night of sleep restriction). Control subjects are shown by the grey dashed line, sleep restricted subjects are graphed in solid black. A) Total sleep time (mins); B) sleep onset latency (mins); C) number of awakenings; D) proportion of total sleep time spent in slow wave sleep; E) proportion of total sleep time spent in REM sleep.

Figure 3. Change in polysomnographic sleep measures across days in the study protocol (B2 – Baseline; SR1 – 1st night of sleep restriction; SR5 – 5th night of sleep restriction). Type 1 subjects are shown by blue circles, Type 2 subjects are graphed in green triangles, and Type 3 subjects are represented by red stars. A) Total sleep time (mins); B) sleep onset latency (mins); C) number of awakenings; D) proportion of total sleep time spent in slow wave sleep (SWS); E) proportion of total sleep time spent REM sleep.

CHAPTER 6: DISCUSSION

The present work set out to examine potential predictors of interindividual vulnerability to the neurobehavioral consequences of chronic partial sleep restriction. The first chapter investigated baseline factors, including neurobehavioral performance while rested, demographics, personality, and intellectual functioning, in relation to changes in psychomotor vigilance following sleep loss. The data show no significant impact of academic achievement, personality, subjective reports of chronotype, sleepiness and fatigue, or performance on other neurobehavioral measures at baseline on change in psychomotor vigilance test (PVT) performance following five consecutive nights of sleep restriction to four hours time in bed. Greater numbers of attentional lapses on the PVT at baseline were consistently associated with larger increases in PVT lapses across chronic sleep restriction. In two of the three analyses, older age was associated with smaller decrements in psychomotor vigilance during chronic partial sleep restriction. This finding replicates prior research demonstrating a positive impact of age on resilience to the effects of sleep loss (Bliese et al., 2006; Landolt et al., 2012; Satterfield et al., 2015). Researchers have suggested that impaired sensitivity of the adenosinergic system in older participants may be implicated in reduced sensitivity to the effects of sleep loss on accumulation of homeostatic sleep pressure and ultimately neurobehavioral performance (Landolt et al., 2012).

Adenosine has been proposed as a physiological marker of sleep need, as it accumulates during wakefulness and inhibits arousal systems (Saper, Scammell, & Lu, 2005). Adenosine receptor antagonists, including caffeine and theobromine, have been identified as effective wake-promoting agents (Boutrel & Koob, 2004). Adenosinergic mechanisms are said to account for as much as 25-50% of the variance in response to sleep loss (Retey et al., 2006). A variant of the adenosine A_{2A} receptor gene (ADORA2A) has been implicated in interindividual differences in neurobehavioral performance during total sleep deprivation and sleep restriction, with

homozygous individuals showing larger declines in performance with increased sleep pressure (Rupp, Wesensten, Newman, & Balkin, 2013). Researchers hypothesized that the effect stems from increased adenosine receptor sensitivity in homozygous individuals, which magnifies the impact of accumulating homeostatic sleep pressure. Findings from studies examining individuals sensitive and insensitive to caffeine, as well as to the effects of countermeasures such as modafinil that have no affinity for the A_{2A} receptors, implicate adenosine as a significant component in understanding interindividual differences in response to sleep loss (Bodenmann et al., 2012; Landolt et al., 2012; Retey et al., 2006). Recent work by Elmenhorst et al linked performance impairment and buildup of homeostatic sleep pressure to an increase in adenosine receptor availability under total sleep deprivation followed by restoration of receptor availability to control levels with extended recovery sleep opportunity (Elmenhorst et al., 2017, 2007). Authors also demonstrated larger increases in receptor availability during sleep deprivation in individuals who were resilient to the effects of sleep loss on performance, suggesting that efficient upregulation of receptors to accommodate the buildup of adenosine during prolonged wakefulness plays an important role in resilience to the effects of sleep loss. Further study of alterations in adenosine receptor density and sensitivity with normative aging and in young adults under conditions of sleep loss is warranted to investigate the modulation of homeostatic sleep pressure and its effect on neurobehavioral performance.

In two of the three analyses in Chapter 1, shorter sleep latency on the Maintenance of Wakefulness Test (MWT) at baseline was associated with greater PVT performance deficits following sleep loss. These findings raise the possibility of an inherent ability to maintain wakefulness in the face of building sleep pressure that may account for a portion of the interindividual differences in neurobehavioral response to sleep loss. Limited data exist on the relationship between MWT and neurobehavioral performance. A study by Rupp et al reported reduced sleep latency on the MWT during total sleep deprivation and sleep restriction that is stable within individuals across multiple exposures to sleep loss (Rupp et al., 2012). There was

significant interindividual variability in performance on the task, such that some individuals were able to consistently maintain wakefulness for the entire duration of the task while others fell asleep very quickly. After controlling for baseline performance on the MWT, the intraclass correlation coefficient increased from 0.54 to 0.63, suggesting a trait-like ability to maintain wakefulness under conditions of sleep loss. Another study examined the relationship between performance on the MWT and the PVT, and found that after two nights of total sleep deprivation, individuals vulnerable to the neurobehavioral effects of sleep loss fell asleep on average eight minutes faster on the MWT than those who were resilient (Frey et al., 2004). However, given several limitations to the study regarding the duration of the MWT and the use of a modified version of the PVT, the findings should be interpreted with caution. The current study of more than three hundred healthy individuals is the first to demonstrate a significant relationship between longer sleep latencies during the MWT at rested baseline and resilience to the effects of chronic partial sleep restriction on PVT performance.

Sleep propensity is often quantified using one of two measures: the Maintenance of Wakefulness Test (MWT) or the Multiple Sleep Latency Test (MSLT) (Michael H. Bonnet, 2006). While performance on the two is correlated, they measure distinct abilities (Sangal, Mitler, & Sangal, 1997; Sangal, Thomas, & Mitler, 1992). The MWT measures the ability to remain awake while sitting in ambient lighting. In contrast, the MSLT instructs individuals to attempt to sleep under soporific conditions. Sleep latencies on the MSLT have been shown to vary by time of day, task environment, prior sleep history, and use of medications, but typically range between 11-12 minutes on average in healthy adults (Bliwise, Carskadon, Seidel, Nekich, & Dement, 1991; M. H. Bonnet & Arand, 2001; Johns, 2000; Steinberg, Schonberg, Weess, Schneider, & Pritzel, 1996; Thorpy, 1992). An alternative MSLT has also been conducted in which individuals are asked to remain awake, as in the MWT, but under soporific conditions. The change in instructions increased average sleep latencies to 12-22 minutes (M. H. Bonnet & Arand, 2001; Michael H. Bonnet & Arand, 2005; Hartse, Roth, & Zorick, 1982). Research has shown that some individuals

can induce or delay sleep depending on task instructions, and demonstrate a short sleep latency on the MSLT and a long latency on the MWT, if they fall asleep at all (Sangal et al., 1992). While short latencies on the MSLT are typically viewed as diagnostic of an underlying sleep condition, given the research thus far it is possible that these individuals have greater control over the sleep-wake maintenance system, and can purposefully initiate sleep or promote wakefulness to meet the demands of their environment.

Research has shown that individuals can be motivated to fall asleep faster or stay awake longer even while sleep deprived (Alexander, Blagrove, & Home, 1991; Harrison, Bright, & Horne, 1996). Shreter et al observed that more than 90% of individuals with untreated sleep apnea and a history of motor vehicle accidents related to falling asleep while driving were able to remain awake for the entire duration of the MWT while undergoing required testing to renew their drivers license (Shreter, Peled, & Pillar, 2006). While not much is known about the role of motivation in the mediation of sleep and wakefulness, animal literature has implicated hypocretin and dopamine in both arousal and motivation, suggesting that internal or external stressors such as hunger, predators, and mating opportunities may promote wakefulness despite homeostatic and circadian signals for sleep in the presence of sufficient motivation (Bonnavion, Jackson, Carter, & De Lecea, 2015; Eban-Rothschild, 2019; Eban-Rothschild, Giardino, & de Lecea, 2017; Mahler, Moorman, Smith, James, & Aston-Jones, 2014; N. E. Taylor et al., 2016; Yamanaka et al., 2003). In the data provided by Shreter et al (2006), it is clear that modern-day external motivations, such as the potential loss of a driver's license, can provide sufficient incentive to maintain wakefulness despite significant predisposition to sleep.

Numerous studies have examined alterations in neuronal activity associated with transitions from wakefulness to sleep under anesthesia, during resting state, or following explicit instructions to try to fall asleep (Chang et al., 2016; Fransson, 2005; Horovitz et al., 2008; Larson-Prior et al., 2009; Poudel, Innes, Bones, Watts, & Jones, 2014; Starbuck, Kay, Platenberg, Lin, & Zielinski, 2000;

Tagliazucchi & Laufs, 2014). Presently, no neuroimaging data exists on the MSLT or the MWT to examine neurological correlates of the ability to maintain wakefulness or induce sleep while rested or under conditions of sleep loss. Simultaneous EEG recording and neuroimaging of the two tasks would provide additional information on brain networks promoting purposeful wakefulness or intentional initiation of sleep. Variable incentives for optimal performance on either task would allow investigators to include motivation and expenditure of effort as additional factors influencing state shifts within the sleep-wake system. Future research to address these topics must examine not only group level effects of motivation and sleep pressure, but also inter-individual differences in the ability to impact changes in sleep-wake state by purposeful regulation of internal alerting signals.

Rothchild et al posited an updated theoretical model for sleep-wake modulation that includes an integrator neuron which weighs all inputs from internal and external environments to decide whether to initiate or terminate sleep. Authors proposed a threshold function to trigger global onset of NREM sleep when enough domains are engaged in local sleep across the brain (Eban-Rothschild, Appelbaum, & De Lecea, 2018). In the context of this new model, interindividual differences in the sensitivity of the integrator neuron, integration latencies, or threshold levels could partially account for differences in vulnerability to the effects of sleep loss. In this view, individuals vulnerable to the accumulation of deficits under sleep deprivation or restriction may be more sensitive to or weight more heavily the accumulation of homeostatic sleep pressure that overrides competing interests such as neurobehavioral task requirements or other external demands for wakefulness. Further research is warranted to investigate the possibility of a modulatory drive in addition to the 2-process model of sleep regulation, as differences within an internal system integrating competing signals for wakefulness and sleep may help inform the present gap in the literature regarding neurobiological mechanisms driving the phenotypic response to sleep loss.

Chapter two examined differences in baseline homeostatic sleep drive and habitual sleep patterns in relation to individual differences in response to sleep loss. Results indicate no significant differences in baseline sleep as measured by polysomnography in the laboratory prior to sleep restriction among individuals who were vulnerable, average, or resilient to the effects of sleep loss as measured by change in PVT performance. Given that the baseline night occurred under strict laboratory conditions, it is possible that it was not an accurate reflection of a typical night of sleep in a home environment, and any group differences were suppressed by standardization of nightly sleep in the laboratory. Examination of habitual sleep patterns outside the laboratory using actigraphy data for the seven days prior to study participation also failed to find significant differences among groups. Vulnerable and resilient participants did not differ on measures of total sleep time, average bedtimes and rise times, or day to day variation in these measures. It should be noted that during this time, participants were asked to keep to a regular sleep schedule that may or may not have corresponded with their preferred timing or duration of sleep.

To address this issue, this study was the first to investigate habitual sleep patterns using actigraphy outside of the laboratory following completion of the sleep restriction protocol. Present data offer a unique chance to observe not only habitual sleep patterns of individuals who are no longer constrained by study participation requirements but also any differential impact of the sleep restriction protocol on habitual sleep. While vulnerability groups did not differ in their habitual sleep durations and timing outside of the laboratory, these sleep measures varied considerably depending on which study protocol individuals completed. Individuals who completed the longest protocol requiring 15-19 consecutive nights in the laboratory with only one night of recovery sleep opportunity prior to departure showed ongoing alterations in their sleep patterns. Participants in that study showed reduced variability in their sleep schedules after leaving the laboratory as compared with individuals who completed 11- and 16-day protocols, both of which also included 2 nights of recovery sleep opportunity of at least 10h time in bed

before departure. This raises the possibility that participants continued to experience increased sleep pressure after completion of the study protocol. Research on long-term consequences of laboratory participation in studies of sleep loss is limited, and little is known about the impact on sleep homeostasis and physiological response. Thus far the focus has been on neurobehavioral recovery following sleep loss and the temporal dynamics of neurobehavioral recovery given varying doses of sleep opportunity. Data indicating a return to baseline levels of neurocognitive performance and subjective reports of sleepiness and fatigue support the idea of functional recovery following study participation given just one night of 10-12 hours of time in bed (Banks, Dongen, et al., 2010; Cohen et al., 2010; Ikegami et al., 2009; Lamond et al., 2007). Until now, no study has followed participants after completion of the protocol to examine whether there is an impact on sleep homeostasis after a brief recovery sleep opportunity in the laboratory. These findings suggest that it may be prudent to investigate any lasting impacts of chronic sleep restriction or total sleep deprivation not only on neurobehavioral performance and subjective reports, but also on the quantity and quality of habitual sleep.

The final chapter examined the relationship between vulnerability to sleep loss and homeostatic response to sleep restriction as measured by polysomnography. Results demonstrate no significant differences among the vulnerability groups. All participants who completed the sleep restriction protocol showed faster sleep onset latencies, fewer nighttime awakenings, and increased proportion of time spent in slow wave sleep. This suggests that all individuals, regardless of phenotypic vulnerability, experience an increase in homeostatic sleep pressure in response to curtailed sleep of just four hours per night. There are several limitations to the present work. The analysis focused exclusively on sleep architecture and did not include power spectral analysis. Prior research has demonstrated trait-like patterns of response in EEG activity during total sleep deprivation and sleep restriction (Tarokh, Dongen, Rusterholz, & Achermann, 2012). It is possible that interindividual differences between vulnerable and resilient individuals may be observed when looking at the various EEG frequencies during the restricted time in bed

opportunity. However, given that prior findings have also failed to find a significant association between changes in power spectral activity and neurobehavioral performance, it is likely that decrements in performance induced by sleep loss stem from factors other than the accumulation of homeostatic sleep drive and rather on the inability to maintain consistent levels of arousal in the face of building sleep pressure (O Tkachenko et al., 2016). Additionally, the current analysis was limited to only the baseline night and the first and fifth nights of sleep restriction. Due to differences in the recovery sleep opportunity following sleep restriction among the study protocols, data from the recovery nights were not included in the analysis. It is possible that if polysomnography data during the recovery sleep opportunity were compared among the vulnerability groups, there may be differences in the rebound effect of the homeostatic system that could not be observed in the limited sleep opportunity during the restriction protocol. Future research should investigate interindividual differences in rebound sleep following total sleep deprivation or chronic partial sleep restriction, and whether individuals differ in the number of recovery days needed to return sleep architecture and spectral power to baseline levels.

The present study includes more than three hundred healthy adults who completed identical protocols of five consecutive nights of sleep restriction under controlled laboratory conditions. Findings indicate no significant impact of personality, academic intelligence, subjective reports of chronotype, sleepiness and fatigue, performance on working memory, and demographic factors such as sex, ethnicity, and body mass index, on vulnerability to the negative effects of sleep loss on psychomotor vigilance. Rather, superior baseline performance on the PVT, older age, and the ability to sustain wakefulness on the MWT were associated with relative resilience to decrements in vigilant attention during sleep restriction. Moreover, interindividual differences in vulnerability to the effects of sleep loss were not accounted for by prior sleep history, habitual sleep patterns outside of the laboratory, baseline sleep architecture, or homeostatic sleep response during chronic partial sleep restriction. Together, these findings suggest that there may be an unknown variable related to the sleep-wake transition process in addition to the homeostatic and circadian

systems. The ability to exert control and willfully mediate shifts between sleep and wakefulness, such that individuals can induce sleep on command under rested conditions and maintain wakefulness in the face of overwhelming sleep pressure, could account for the observed lack of differences in homeostatic response to sleep restriction and offer further insight to the mechanisms driving phenotypic vulnerability to sleep loss.

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