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**Wired to Sleep on it: Interactions between Structural Neuroanatomy, Sleep Oscillatory Acivity, and Hippocampal-Dependent Learning and Memory**

by

Jared Meyer Saletin

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy

in

Psychology

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Matthew P. Walker, Chair
Professor Ronald E. Dahl
Professor Arthur P. Shimamura

Spring 2014

**Wired to Sleep on it: Interactions between Structural Neuroanatomy, Sleep Oscillatory Acivity, and Hippocampal-Dependent Learning and Memory**

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Jared Meyer Saletin

## Abstract

Wired to Sleep on it: Interactions between Structural Neuroanatomy, Sleep Oscillatory Acivity, and Hippocampal-Dependent Learning and Memory

by

Jared Meyer Saletin

Doctor of Philosophy in Psychology

University of California, Berkeley

Professor Matthew P. Walker, Chair

Sleep is highly conserved across phylogeny, yet marked inter-individual differences in sleep physiology are expressed. In humans, such variability is especially evident for non-rapid eye movement (NREM) sleep spindle and slow wave oscillations, representing trait-like physiological "fingerprints". Nevertheless, the mechanisms accounting for these differences, and the functional consequences of this variability, remain largely unknown. This thesis combines structural MRI, sleep EEG, and cognitive memory paradigms to test the hypothesis that brain morphology represents one candidate factor explaining inter-individual differences in NREM oscillations, which, in turn, consequently predict functional learning and memory. From this central hypothesis, three inter-related, yet distinct, studies are presented. **Study 1** demonstrates that inter-individual variability in NREM physiology is accounted by grey matter morphology in functionally relevant brain regions. Specifically, grey matter in the sleep-regulating center of the basal forebrain/hypothalamus, together with the medial prefrontal cortex, accounted for individual differences in NREM slow waves. In contrast, grey matter in interoceptive and exteroceptive cortices predicted slower NREM sleep spindles, whereas grey matter volume in bilateral hippocampus was associated with faster sleep spindles. **Study 2** establishes that the substructure of the hippocampus—specifically, the CA3/DG subfield—determines inter-individual levels of learning impairment following sleep deprivation, yet conversely interacts with post-deprivation recovery NREM sleep in predicting learning restoration. Finally, **Study 3** describes a beneficial influence of fast NREM sleep spindles on differentially gating the selective offline consolidation of memories, based on prior waking instructions, leading to the selective remembering and forgetting of discreet item information. Together, these data indicate that macroscopic differences in structural brain morphology represent one mechanism accounting for individual differences in NREM sleep physiology, as well as associated consequences for learning and memory. More generally, these findings offer translational relevance to the structural brain abnormalities present in conditions such as dementia, sleep apnea, attention-deficit hyperactivity disorder, and post-traumatic stress disorder, where sleep disruption and memory impairment are highly co-morbid.

In dedication to my loving and giving grandparents:
Ballard, Clementine, Nathan, and Yetta.

*Even a soul submerged in sleep is hard at work and helps make something of the world.*

– Heraclitus, *Fragments*

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# Introduction

*Even a soul submerged in sleep is hard at work and helps make something of the world.*

– Heraclitus, *Fragments*

## Sleep and associated oscillatory activity

Sleep—classically defined as a quiescent yet rapidly reversible behavioral state—occupies nearly one-third of human life (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Across a single night, the brain progresses through a series of sleep stages—each with its own neurophysiology (Steriade, 2006), neurochemistry (Jones, 2005) and functional neuroanatomy (Dang-Vu, Schabus, Desseilles, Sterpenich, et al., 2010). In mammalian species, sleep has been broadly separated into two main types: non-rapid eye movement (NREM) sleep (which, in humans, is further separated into NREM stages 1—4; increasingly with depth of sleep), and rapid eye movement (REM) sleep. These established stages of sleep are characterized by stereotypical features of electroencephalographic (EEG) brain activity, from which different functional benefits of sleep emerge. Within the EEG signatures of sleep NREM is defined by a progressive slowing of the EEG from wakefulness (dominated by frequencies of the Alpha range (8–12 Hz) and higher) to the theta waves (4–8 Hz) of "Stage 2 NREM" to the eventual deep "Slow Wave Sleep" (Stages 3 and 4 NREM), dominated by Delta waves in the 0.5–4 Hz range. These slow waves, representing gross synchrony across large populations of neocortical neurons, are accompanied by phasic short bursts of faster activity known as sleep spindles (e.g. 11–15 Hz; 2 seconds in length) that emerge from mutually inhibitory thalamocortical circuitry (Steriade, 2006). Together, these slow waves and sleep spindles form the milieu of NREM brain activity, one that dominates two thirds of a night of sleep.

## Inter-individual differences among NREM oscillations

While these general patterns of NREM oscillatory activity are conserved across mammalian phylogeny as well as within-species ontogeny, remarkable inter-individual differences in are expressed. In humans, such physiological variability is especially evident for non-rapid eye movement (NREM) sleep spindle and slow wave oscillations, argued to representing a trait-like individual sleep "fingerprint" (De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005). This variability exists for both slow waves and sleep spindles alike. Slow waves vary between indi-

viduals in their magnitude (amplitude) and their incidence (Carrier et al., 2011). Similar inter-individual differences are observed in the homeostatic rebound of slow wave activity following sleep deprivation—a marker of sleep pressure and the recovery from sleep loss (Modirrousta, Mainville, & Jones, 2007).

Sleep spindles demonstrate similarly pronounced variability across individuals, both in the slower (about 11–13 Hz) and faster (about 13–15 Hz) frequency range (De Gennaro & Ferrara, 2003). Indeed, this frequency range is one of the most distinct spindle features to express individual differences, with some individuals occupying the "faster" tail of the frequency distribution (with frequencies ranging closer to 15 Hz, on average), while others demonstrate markedly "slower" spindles (with mean frequencies closer to 12–13 Hz) (Werth, Achermann, Dijk, & Borbély, 1997).

While such individual differences in sleep physiology have been well documented, the explanatory mechanisms underlying this variability remain largely unknown. Moreover, such stable variability is rarely considered in the context of influencing the known functional benefits of NREM sleep upon brain function, especially learning, memory and brain plasticity.

## Benefits of sleep on hippocampus-dependent learning and memory

This thesis principally focuses on the interaction between sleep and hippocampus-dependent memory processing at two memory stages: both before learning, in preparation for in initial memory encoding, and after learning, in the offline consolidation of memory—the existing evidence for which offers important foundational knowledge motivating the current studies.

### Sleep before learning to support memory formation

Consistent with cellular and molecular investigations demonstrating disrupted hippocampal cellular plasticity (Abel, Havekes, Saletin, & Walker, 2013), total sleep deprivation in humans markedly impairs medial temporal lobe activity during attempted memory encoding (Drummond et al., 2000). Moreover, one night of total sleep deprivation impairs encoding-related activity specifically within the hippocampus, associated with a near 50% reduction in learning success (Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Furthermore, selective deprivation of NREM slow waves alone is sufficient to induce similar hippocampal encoding impairments and associated learning deficits (Van Der Werf et al., 2009). Thus, functional mechanisms of learning within the hippocampus appear to be especially sensitive to the disruptive impact of sleep loss, and of NREM sleep disruption in particular. In contrast, the presence of sleep, and specifically the quantity/quality of NREM sleep spindles (Mander, Santhanam, Saletin, & Walker, 2011) and slow waves (Antonenko, Diekelmann, Olsen, Born, & Mölle, 2013) activity predict the post-sleep restoration of hippocampal-dependent encoding and associated learning capacity.

Despite the evidence that sleep loss dramatically impairs hippocampus-dependent learning, marked variability in the degree of this impairment exists across individuals, the underlying mechanisms of which are poorly understood. Characterizing such inter-individual mnemonic vulnerability (or converse resilience) is important for at least two reasons: First, identifying the

determinants of these differences—here proposing regional brain anatomy (as described below)—may inform the basic mechanisms leading to impaired learning under conditions of sleep loss. Second, and critically important at a translational level, such mechanistic evidence may aid researchers in predicting the severity of impairments observed in those individuals who routinely subject themselves to short sleep restrict sleep (e.g., military, transportation, and medical professions) (Czeisler, 2011).

## The need of sleep after learning to support memory consolidation

Not only is sleep before learning necessary for encoding, but sleep after learning appears critical for offline memory consolidation. Early behavioral evidence in humans established that sleep, and specifically NREM sleep, preferentially stabilized recently learned hippocampal-dependent memory, minimizing forgetting (Jenkins & Dallenbach, 1924). Moreover, inter-individual differences in both slow waves (Marshall, Helgadóttir, Mölle, & Born, 2006) and sleep spindles (Schabus, Gruber, et al., 2004) after learning predict the success of memory consolidation, as measured by later recall ability.

The dynamics of memory consolidation during sleep have been suggested to rely on a spindle-mediated "reactivation" of memories during sleep. Hippocampal place-cells recapitulate their patterns of learning activity during cortical sleep spindle events (Abel et al., 2013). Supporting this role of sleep spindles in memory consolidation, electrical stimulation during NREM sleep potentiates not only slow waves but also sleep spindle activity, leading to memory consolidation (Marshall, Helgadóttir, et al., 2006). Moreover, increases in functional connectivity are observed between the human hippocampus and the neocortex during spindle events themselves (Andrade et al., 2011)—consistent with the strengthening of neocortical memory representations across sleep; leading to successful memory consolidation.

While at first counterintuitive, the capacity to forget can, in certain contexts, be as important as the need to remember. One context where this is particularly relevant is within clinical populations (e.g. post-traumatic stress disorder and addiction) where aberrant long-term retention of trauma memories (Acheson, Gresack, & Risbrough, 2012) can lead to impaired prolonged anxiety. Sleep may support a role in this selective memory consolidation. Indeed, offline periods of sleep result in superior retention of emotional (salient) memories compared to neutral memories (Wagner, Gais, & Born, 2001; Hu, Stylos-Allan, & Walker, 2006; Nishida, Pearsall, Buckner, & Walker, 2009). However, the mechanisms by which sleep can selectively discern which memories are to be consolidated, and which are to be forgotten, remain under investigated. One testable hypothesis to be examined in the current thesis, and one that expands on the broader role of sleep in memory consolidation, is that sleep spindles benefit memory consolidation, not generally across all memories, but in a manner sensitive to the salience of learned information.

## Brain structure as a candidate determinant of NREM variability and associated function

The current thesis proposes that regional structural morphology of the brain is one novel candidate factor that not only predicts inter-individual differences in NREM physiology, but also determines the functional consequences on processes of memory as a result (both encoding and consolidation). This central hypothesis is motivated by several lines of evidence. First, it is well known that the structural of the nervous system is a strong determinant of its function (Kanai & Rees, 2011), including learning and memory (Lee, Ekstrom, & Ghetti, 2014). Second, within the context of the human brain, these structural-functional relationships extend beyond healthy adults, being further observed in circumstances of early development (Wendelken, Lee, et al., 2014), late life deterioration (Wirth et al., 2013), brain damage (Fogelson, Shah, Scabini, & Knight, 2009) and disease (Nho et al., 2012). Third, individual-differences in NREM sleep EEG appear critically predictive of the success of memory processing (Abel et al., 2013). Fourth, these NREM slow waves and sleep spindles have established functional neuroanatomical correlates (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008; Schabus, Dang-Vu, et al., 2007) that overlap with the functions of the oscillations themselves (e.g. hippocampus BOLD activity during memory-related spindle activity). Despite these lines of evidence linking brain structure to brain function, and sleep EEG to brain function, no study has yet characterized whether brain structural morphology may account for individual differences in sleep physiology.

Integrating across these findings, this thesis combined structural neuroimaging, whole-head sleep EEG recordings, and hippocampus-dependent memory paradigms across three studies to examine a central hypothesis: that individual differences in the expression and functional memory consequences of NREM sleep are determined by underlying variability in regional brain morphology. Three experiments flow from this central thesis: **Study 1** combines a full night of rested sleep EEG with high-resolution structural grey matter imaging to explore the structural predictors of NREM slow waves and sleep spindles. **Study 2** employs a sleep deprivation paradigm to examine how variability in hippocampus structures predicts the degree of impairments in learning following sleep deprivation. Further, motivated both by findings that deprivation-impairments in memory are explicitly linked to slow waves (Van Der Werf et al., 2009) and the well-known role of slow waves in homeostatically regulating the recovery from sleep deprivation (Modirrousta et al., 2007), we examine whether the same hippocampus structural variability at all determines the degree of NREM slow wave-mediated restoration in learning following a bout of recovery sleep. Finally **Study 3** examines the sensitivity of sleep to selective memory consolidation as determined by inter-individual variability in sleep spindles. Particularly we focus on the specific class of sleep spindle identified in **Study 1** as being determined by memory-relevant anatomy.

# Chapter 1

# The Structural Neuroanatomical Correlates of NREM Sleep Oscillations

Sleep is strongly conserved within species, yet marked inter-individual differences in sleep physiology are observed. Combining EEG sleep recordings and high-resolution structural brain imaging, here we demonstrate that the morphology of the human brain offers one explanatory factor of such inter-individual variability. Grey matter volume in interoceptive and exteroceptive cortices correlated with the expression of slower NREM sleep spindle frequencies, supporting their proposed role in sleep protection against conscious perception. Conversely, and consistent with an involvement in declarative memory processing, grey matter volume in bilateral hippocampus was associated with faster NREM sleep spindle frequencies. In contrast to spindles, grey matter volume in the homeostatic sleep-regulating center of the basal forebrain/hypothalamus, together with the medial prefrontal cortex, accounted for individual differences in NREM slow wave oscillations. Together, such findings indicate that the qualitative and quantitative expression of human sleep physiology is significantly related to anatomically specific differences in macroscopic brain structure.

## 1.1 Introduction

Sleep is strongly conserved across phylogeny. In humans, sleep EEG physiology is remarkably stable within an individual from one night to the next (Werth, Achermann, et al., 1997). However, striking differences in these same sleep EEG features are observed from one individual to the next (De Gennaro, Ferrara, et al., 2005), the reasons for which are largely unknown. Most prominent are inter-individual differences in non-rapid eye movement (NREM) sleep, specifically slow waves (Mongrain et al., 2006; Tucker et al., 2007; Viola et al., 2012) and sleep spindles (De Gennaro, Ferrara, et al., 2005; Werth, Achermann, et al., 1997). Furthermore, these sleep EEG features demonstrate evidence of partial genetic determination (Vandewalle et al., 2009; Viola, Archer, et al., 2007), further suggesting they represent a stable, trait-like physiological phenotype. Here, we examine one potential factor explaining these trait inter-individual differences in sleep EEG physiology—brain structure. The morphology of the brain is a known determinant of function, evidenced by circumstances of development, degeneration, and brain damage (Kanai & Rees, 2011). Despite such relationships, the possibility that individual differences in human brain structure predict individual differences in sleep physiology remains largely uncharacterized.

Although limited structural evidence exists, candidate anatomical regions of interest that may in turn explain individual differences in sleep spindles and slow waves emerge from their proposed functional roles (e.g. learning and memory) or their functional and/or electrical source generators. For example, sleep spindles have been implicated in the inhibitory "gating" of exteroceptive and interoceptive sensory perception (De Gennaro, Ferrara, et al., 2005), thereby preserving the sleep state from both exogenous (e.g. audition (Dang-Vu, Schabus, Desseilles, Sterpenich, et al., 2010)) and endogenous (e.g. pain (Landis, Lentz, Rothermel, Buchwald, & Shaver, 2004)) disruption. This protective function appears to be dependent upon mutually-inhibitory reticulothalamic-cortical circuitry (Contreras, Destexhe, Sejnowski, & Steriade, 1996; De Gennaro & Ferrara, 2003), implicating the thalamus, and its surrounding nuclei, as potential structural region of interests (ROIs) accounting for differences in trait-varying properties of sleep spindles. Related, connected cortical areas where processing of such exogenous and endogenous stimuli that pose the greatest likelihood of sleep disruption, namely auditory cortex and insular cortex, respectively, offer additional functionally-relevant ROIs. Indeed, functional neuroimaging has described activation in both primary auditory (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008) and insula cortices (Schabus, Dang-Vu, et al., 2007) during the occurrence of sleep spindle events. Finally, and contrasting with a sleep-protective function, an emerging role assigned to sleep spindles—and particularly those of fast frequencies (e.g. greater then 13 Hz)—is the processing of hippocampal-dependent memories (Abel et al., 2013). Inter-individual differences in faster frequency sleep spindles predict hippocampal-dependent learning ability (Mander, Santhanam, et al., 2011) following sleep, as well as being implicated in the consolidation of prior learned memories (Mölle, Bergmann, Marshall, & Born, 2011). Furthermore, faster frequency sleep spindle events coincide with hippocampal activation, as assessed by event-related fMRI (Schabus, Dang-Vu, et al., 2007).

As with spindles, target anatomical regions that may contribute to inter-individual difference in slow wave features are informed by reports examining the functional properties of slow waves

(including density and amplitude). Slow waves are the canonical marker of sleep homeostatic processes within the EEG. The basal forebrain, therefore, represents one such candidate due to its well-defined role in sleep homeostasis and regulation (Modirrousta et al., 2007) and regulating changes in slow wave density following prolonged wakefulness (Mistlberger, Bergmann, & Rechtschaffen, 1987). Beyond the basal forebrain, midline prefrontal cortex and insula cortex both represent additional target regions accounting for slow wave differences between individuals, particularly their amplitude. For example, slow waves are not simply dominant over topographic midline prefrontal EEG derivations (Feinberg & Floyd, 1979), but these frontal derivations also display the greatest extent of inter-individual variability in slow waves as a function of genotype (Viola, Chellappa, et al., 2012) and chronotype (Mongrain, Carrier, & Dumont, 2006). Moreover, inter-individual differences in the homeostatic rebound of slow waves following sleep deprivation are similarly observed in the EEG over midline prefrontal cortex (Goel, Banks, Mignot, & Dinges, 2009; Rusterholz & Achermann, 2011). Consistent with this scalp pattern of frontal topography, source analyses of the EEG slow wave signal have localized source generators in cingulate cortex, consistent with a midline prefrontal dominance of slow waves (Murphy et al., 2009). These analyses also revealed the insula cortex as a primary source-generator of slow waves (Murphy et al., 2009). The known cytoarchitecture of the insula cortex and its connectivity to prefrontal cortex has therefore been proposed to support propagation of slow waves between these potential generator regions (Petrides & Pandya, 1999; van der Kooy, McGinty, Koda, Gerfen, & Bloom, 1982).

Guided *a priori* by these candidate regions here we examine whether macroscopic differences in human brain structure, indexed by grey matter volume, explain stable inter-individual variability (De Gennaro, Ferrara, et al., 2005) in the canonical oscillations of sleep: sleep spindles and slow waves.

## 1.2 Materials and Methods

Twenty-two healthy adults (21.2 ± 2.25 years [mean ± sd], (range 19–26), 10 males) participated in the study. Exclusion criteria, assessed using a pre-screening questionnaire, included a history of sleep disorders, neurologic disorders or closed head injury, Axis I psychiatric disorders according to the DSM-IV criteria encompassing major mental disorders, history of drug abuse, and current use of anti-depressant or hypnotic medication. Participants abstained from alcohol and caffeine for a minimum of 48 hours prior to sleep recording. Additionally, sleep schedules were standardized prior to in-lab recordings (7–9 h of sleep per night, with morning wake time between 06:30 and 08:30), as verified by nightly sleep logs. The study was approved by the local human studies committee, with all participants providing their written informed consent.

### Polysomnography recording and sleep stage classification

Polysomnography (PSG) sleep monitoring was recorded using a Grass Technologies Comet XL system (Astro-Med, Inc., West Warwick, RI). Electroencephalography (EEG) was recorded at 19

standard locations conforming to the International 10-20 System (Jasper, 1958) (FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). Electrooculography (EOG) was recorded at the right and left outer canthi (right superior; left inferior). Electromyography (EMG) was recorded via three electrodes (one mental, two sub-mental). Finally, electrocardiography (ECG) was recorded using two electrodes: below the left and right clavicle. Reference electrodes were placed at both the left and right mastoid (A1, A2). Data were digitized at 400Hz. All data were stored unfiltered (recovered frequency range of 0.1–100 Hz), except for a 60Hz notch filter. For recording only, each channel was referenced to a forehead scalp reference. Sleep staging was performed in accordance with standardized techniques (Rechtschaffen & Kales, 1968) from the C3-A2 derivation, and NREM-REM cycles were defined according to modified criteria of Feinberg and Floyd, 1979 (Aeschbach & Borbély, 1993). Sleep statistics for both sleep continuity and sleep architecture are reported in **Table 1.1**; revealing normative sleep patterns for this age-group (Ohayon et al., 2004) during the night of laboratory-recorded sleep.

## Polysomnography EEG signal processing

Following sleep scoring, each EEG channel was re-referenced to the average of the left and right mastoids for quantitative signal processing. All EEG analyses were performed in MATLAB 7.5 (The Mathworks, Natick, MA), including the add-in toolbox EEGLAB http://sccn.ucsd.edu/eeglab/. The EEG was band-passed filtered offline (EEGLAB function eegfilt) using Finite Impulse Response (FIR) filters (low-pass at 50Hz, high-pass at 0.5Hz). A high-pass cutoff frequency of 0.5 Hz was chosen to remove possible slow artifact in the EEG. Signals were then visually marked for artifact in 5-second epochs. Each 5-second epoch of data used for artifact-rejection was matched its corresponding scored sleep.

Slow waves were detected using an established procedure (Kurth et al., 2010; Massimini et al., 2007; Murphy et al., 2009; Riedner et al., 2007). Following artifact rejection, a low-pass FIR filter was applied to EEG data removing all activity above 4Hz (yielding a frequency distribution of (0.5–4 Hz, as in previous slow wave detection analyses) (Kurth et al., 2010; Massimini et al., 2007; Murphy et al., 2009; Riedner et al., 2007). In short (but see (Riedner et al., 2007) for details) the algorithm determines negative and positive peaks occurring in the EEG time series after each zero-crossing (change in amplitude from negative-to-positive, or vice-versa), detecting slow waves in each channel independently. Multiple peaks occurring between zero-crossings were considered part of the same slow wave. Waves were then sorted according to sleep stage. Any detections occurring during Stage 1 were excluded from analysis. Further, analyses were limited only to defined NREM periods (Aeschbach & Borbély, 1993). Finally, all waves occurring within artifact-marked epochs were removed from analysis. Analysis of slow waves focused on two orthogonal metrics—amplitude and density, respectively. Of note, slow wave activity (SWA; power in the 0.75–4.75 Hz band) was not chosen in the current study since this composite spectral measure cannot distinguish between the amplitude of slow waves and their incidence (density) (Carrier et al., 2011). For slow wave amplitude, the negative peak (μV) of each NREM slow wave was averaged to create a single NREM average for each EEG channel, in each subject. Slow wave density was calculated as the number of artifact-free detected slow waves in each channel

divided by the amount of artifact-free NREM sleep time recorded, resulting in a single NREM value for each EEG channel, in each subject. Both slow wave metrics were then included in the MRI regression analyses, with parameters derived from the Fz (frontal midline) EEG derivation chosen, due to the known topography and concentration of slow waves over midline frontal cortex, both in the current study (**Fig. 1.2**), and prior reports (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008; Kurth et al., 2010; Murphy et al., 2009; Riedner et al., 2007).

In parallel, sleep spindles were detected for each channel of EEG by an established automatic algorithm (Ferrarelli et al., 2007; Mander, Santhanam, et al., 2011; Saletin, Goldstein, & Walker, 2011). Band-pass FIR filters were first applied to EEG sleep data (spindle range: high-pass: 11 Hz; low-pass: 15 Hz), restricting detection to only those events falling within the spindle frequency range (11–15 Hz) (Schabus, Dang-Vu, et al., 2007). NREM epochs were extracted (NREM stages 2, 3 and 4) based on visual scoring and all artifact-free epochs were concatenated into one continuous NREM time series for analysis. The amplitude of the rectified signal from NREM sleep was used as a unique time series, identifying amplitude fluctuations exceeding channel-wise threshold values, with the lower and upper values set at two and eight times the average amplitude for each channel separately. The boundaries of spindle events were then defined when amplitude fluctuations dropped below the cut-off threshold. For each participant, spindle frequency was calculated for each spindle defined as the number of peaks in the EEG signal occurring within the spindle event, divided by the duration of the spindle, yielding a frequency measure in cycles per second (Hz). These analyses focused specifically on spindle frequency, rather then features such as amplitude or density, as it is frequency that demonstrates the stable trait-like inter-individual differences previously described to form a spindle "fingerprint" across individuals (De Gennaro, Ferrara, et al., 2005; Werth, Dijk, Achermann, & Borbély, 1996). Therefore, channel-wise average spindle frequency was determined for NREM sleep by averaging the frequencies of each detected spindles, within each channel, respectively. However, it is important to note the heterogeneity of spindle frequency across the scalp. Slow spindles are frontal dominant, while fast spindles show parietal dominance (De Gennaro & Ferrara, 2003; Mander, Santhanam, et al., 2011; Saletin et al., 2011; Schabus, Dang-Vu, et al., 2007). To most fully describe the individual-wise frequency "setpoint'' we examined spindles within the entire spindle frequency range (11–15 Hz). In an attempt to remove any influence of topography on subject-wise metrics of spindle frequency, frequency estimates were then subsequently averaged over traditional midline electrodes (frontal (Fz), central (Cz) and parietal (Pz), rather than using any one single electrode for analysis. This average allowed for the characterization of an individuals' average spindle frequency across the anterior/posterior head axis; allowing for equal contribution of slow and fast spindle frequencies over different cortical regioFzns. Following averaging, each individual's representative spindle frequency was used in structural imaging regression analyses.

## EEG source localization of slow waves

Given the well-documented source generators of slow waves (Murphy et al., 2009), described above, were performed to assess whether potential structural brain correlates of NREM slow waves converged with homologous regions of electrical generation. To this end, standardized

low resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) was calculated for the negative peak of the slow wave, as described below. The sLORETA approach to source analysis computed solutions using a head model based on the MNI152 template (Mazziotta et al., 2001). Solution space is limited to cortical grey matter, making sLORETA more precise than other methods of source localization that are not anatomically constrained, and is made up of 6239 voxels at 5 mm resolution (Pascual-Marqui, 2002). While the anatomical precision of sLORETA, and of all source analysis techniques, varies depending on the number of electrodes in the EEG montage (Laarne, Tenhunen-Eskelinen, Hyttinen, & Eskola, 2000), numerous studies have employed source analysis using montage arrays of similar or lower resolution to the current study, indicating sufficient coverage of the scalp to provide robust source estimates (Bela, Monika, Marton, & Istvan, 2007; Clemens, Bank, et al., 2008; Clemens, Piros, et al., 2009; Isotani et al., 2001; Pascual-Marqui et al., 1999; Ponomarev, Gurskaia, Kropotov Iu, Artiushkova, & Muller, 2010; Tislerova et al., 2008; Veiga et al., 2003). Interpretation of sLORETA findings is limited to the lobular level of resolution, and not beyond, fitting with prior expectations of this array density (Bela et al., 2007; Clemens, Bank, et al., 2008; Clemens, Piros, et al., 2009; Isotani et al., 2001; Pascual-Marqui et al., 1999; Ponomarev et al., 2010; Tislerova et al., 2008; Veiga et al., 2003). Consistent with previous EEG source analyses of slow waves (Murphy et al., 2009), NREM filtered (0.5–4 Hz) was marked at the maximal negative peak of each slow wave detected at Fz. In an event-related potential approach, 1-second epochs were extracted around the negative peak (500 ms on either side). Each epoch, corresponding to one wave, was averaged within- and then between-subjects, yielding a single grand-average epoch for the group (variability of individual participant's Fz average epoch depicted in **Fig. 1.2**). Finally, this 1-second epoch was submitted to sLORETA analyses in the time-domain. Source localization was centered on the negative peak of the grand-average waveform.

## Structural magnetic resonance imaging

Structural MRI was performed on a Siemens Magnetom Trio 3T scanner equipped with a 32-channel head coil. Two concomitant high-resolution MPRAGE T1-weighted anatomical scans were obtained for each participant, each consisting of 176 sagittal slices (1 mm isotropic voxels) acquired with a repetition-time (TR) of 2300 ms and an echo-time (TE) of 2.52 ms. Individual estimates of grey matter volume, a stable trait-like measure previously demonstrated to offer sensitivity to inter-individual variability in brain morphology (Thompson et al., 2001), was calculated using the validated voxel-based morphometry approach (VBM) (Ashburner & Friston, 2000; Dumontheil, Houlton, Christoff, & Blakemore, 2010; Ridgway et al., 2009). VBM analysis quantified the signal intensity of each voxel in the brain for a grey matter segmentation image, given the differential signal intensity yielded by magnetic resonance properties of grey and white matter, respectively. These grey matter voxel intensities were entered into whole-brain regression analyses, comparing grey matter volume and a given experimental variable, in this case, sleep EEG physiological parameters. While other methods for grey matter imaging exist, allowing for manual (Neylan et al., 2010) or semi-automated segmentation of brain volumes (Schmidt et al., 2006), the VBM procedure has been repeatedly used and validated for whole-brain imaging of

voxel-wise grey matter volume (Celle et al., 2010; Dumontheil et al., 2010; Giorgio et al., 2010; Mueller et al., 2011; Pereira et al., 2010; Ridgway et al., 2009).

Image processing used Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm) in conjunction with the VBM 5.1 Toolbox for SPM5 (http://dbm.neuro.uni-jena.de/vbm/). To maximize signal-to-noise, and therefore the ability to detect structural differences between participants, the two anatomical T1-weighted MPRAGE scans were first realigned (SPM8 Realign: 2nd Degree B-Spline Interpolation) to each other and then averaged. One participant contributed only 1 scan, due to technical issues during acquisition. Segmentation of anatomical images into grey matter (GM), white matter (WM) and cerebral spinal fluid (CSF) was estimated for each participant's mean anatomical scan using the VBM5.1 Toolbox, implementing default settings (Koutsouleris et al., 2009), including iterative weighting of a hidden markov random field (HMRF). While the standard SPM segmentation uses prior information to estimate the tissue classes of each voxel, VBM5.1 uses a Bayesian approach not dependent on tissue priors, which can allow for greater accuracy in tissue segmentation (Koutsouleris et al., 2009). Following segmentation, DARTEL was used in SPM8 (Ashburner, 2007) to generate a study-specific group template average using standard procedures, including 6 iterations of template fitting, and the use linear elastic energy for regularization. Following template registration, this template was normalized to MNI space and the resulting transformation matrix was used to normalize the DARTEL flow fields and individual tissue images of all 22 subjects into standard space (DARTEL routine: "Normalise to MNI Space"). The normalization maintained a voxel size of 1 mm isotropic, included modulation to preserve regional signal intensities, and included a 8 mm Gaussian FWHM smoothing-kernel to reduce signal-to-noise for statistical analyses.

An explicit thresholding mask based on the signal-to-noise of the data was calculated according to prior procedures (Ridgway et al., 2009), optimizing the threshold of each individual's grey matter image given the distribution of data across the group as a whole, aiming to remove low-signal noise from analyses. Finally, total intracranial volume (TIV) was calculated from each participant's native-space GM, WM, and CSF segmentations calculated from VBM5.1. Total intracranial volume was calculated from the native-space tissue maps according to the "get_totals" routine for SPM commonly used to calculate global measures of brain volume in structural imaging studies (e.g. (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012; Benedetti, Radaelli, et al., 2011; Benedetti, Poletti, et al., 2012; Eckert et al., 2008; Wolk et al., 2009), etc.). Cross-sectional analyses of EEG data raise concerns of differences in skull thickness that, beyond the electrical signal itself, could lead to amplitude differences. However, considering that the variance of EEG amplitude explained by skull thickness across frontal, temporal and parietal regions ranges from $r^2$ = 0.01 to $r^2$ = 0.13 (Hagemann, Hewig, Walter, & Naumann, 2008) it would suggest any such contribution is likely modest.

## Statistical analyses

To examine the bidirectional nature of inter-individual difference in sleep spindle frequency, positive and negative contrast maps were generated, reflecting areas where grey matter volume correlated with increasingly faster, or slower spindle frequency, respectively. Slow wave regression

models were then created for the average negative amplitude of the slow waves, and the density of slow waves, in NREM sleep, respectively. For each slow wave model, positive and negative contrast maps were created. This analysis employed separate statistical models for each analysis to minimize the impact of co-linearity between sleep spindles and slow waves (Steriade, McCormick, & Sejnowski, 1993) and between specific properties of slow waves themselves (Carrier et al., 2011). For slow wave analyses, one subject was removed from the regression (yielding n = 21) based on prominent artifact in their recording within the slow wave frequency range (about 0.6 Hz). In all statistical models, proportional scaling to TIV (total intracranial volume) was used to account for total brain size, as in previous VBM studies (Bendlin et al., 2008). The current results did not change when age was included as an additional covariate in the model.

Statistical analysis was performed using a two-step approach, as in previous studies (Altena, Vrenken, Van Der Werf, van den Heuvel, & Van Someren, 2010; Gong et al., 2005; Joo, Tae, Kim, & Hong, 2009; Joo, Tae, Lee, et al., 2010; Kim et al., 2008; O'Donoghue et al., 2005; Yaouhi et al., 2009). First, at the whole-brain level, uncorrected results were identified at a voxel-wise p-value of 0.001 (30 voxel extent threshold), followed next by analysis of clusters within candidate ROIs that survived this initial threshold. These clusters were subsequently submitted to small volume correction (SVC) at the family-wise-error rate of $p < 0.05$, cluster level (Joo, Tae, Kim, & Hong, 2009; Kim et al., 2008; Yaouhi et al., 2009; Nichols & Hayasaka, 2003). This two-step analysis approach allowed both for a strict test of our hypothesis-driven ROIs targets, while still offering an exploratory investigation of associations outside these ROIs; important considering the current study represents the first investigation of structural grey matter associations with sleep EEG physiology in the adult brain. Figures were generated by overlaying statistical images on ch2better.nii.gz template provided in the MRIcron visualization software, in standardized space. Images for display were thresholded at a $p < 0.005$.

## Definition of small volume correction (SVC) regions of interest (ROI)

For slow wave regression models, SVC was performed on *a priori* anatomical ROIs derived from convergent source EEG analyses (Murphy et al., 2009) and functional neuroimaging studies (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008; Maquet et al., 1997), resulting in ROIs in bilateral cingulate, insula (anterior and posterior) and orbital frontal cortices (defined within the validated wfu_pickatlas SPM toolbox (http://www.fmri.wfubmc.edu/cms/software) (Maldjian, Laurienti, Kraft, & Burdette, 2003). These areas are congruent with the both the results of EEG source analyses (Murphy et al., 2009), as well as known topography dominance of slow waves and their inter-individual differences occurring over midline frontal cortex (Carrier et al., 2011; Esser, Hill, & Tononi, 2007; Feinberg, de Bie, Davis, & Campbell, 2011; Huber, Ghilardi, Massimini, & Tononi, 2004; Mongrain et al., 2006; Murphy et al., 2009; Rusterholz & Achermann, 2011). Finally, an ROI mask in the region of the basal forebrain and hypothalamus was created, identified from neurophysiology studies demonstrating it as the seat of sleep-wake regulation (Kalinchuk, McCarley, Porkka-Heiskanen, & Basheer, 2010; Modirrousta et al., 2007; Monti, 2011), a process that is represented by slow waves in the EEG (Esser et al., 2007; Tononi & Cirelli, 2006), as well as from neuroimaging findings demonstrating associations between the basal fore-

brain/hypothalamus and slow wave activity (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008; Maquet et al., 1997). The ROI was defined by creating 8 mm diameter sphere around previously published coordinates from a functional neuroimaging study of slow waves sleep (MNI voxel coordinates [x, y, z]: [2, 2, -4]) (Maquet et al., 1997). The choice of a sphere defined functionally, rather than the use of an anatomical ROI was based upon the known heterogeneity of function within the anatomical region of the basal forebrain/hypothalamus that prevents the anatomical delineation of sleep-related nuclei at the resolution of structural MRI (Maquet et al., 1997; Szymusiak, 1995). For the purpose of statistical inference, these ROIs were considered independent tests based on differential anatomical networks implicated in the generation and regulation of each different physiological oscillation.

A similar approach was followed for sleep spindles. Specifically, ROIs were created based on *a priori* regions of interest, also using the wfu_pickatlas toolbox. First, based on well-described animal neurophysiology (Steriade, Deschênes, Domich, & Mulle, 1985) and human functional neuroimaging studies (Schabus, Dang-Vu, et al., 2007) indicating the thalamus in spindle generation, bilateral thalamic ROIs were created. Second, sensory ROIs were constructed building on the proposed role of sleep spindles in protecting sleep against external and internal conscious sensation. ROIs focused on the anatomical cortical regions associated with the two sensory percepts most prevalent to sleep disruption: exteroceptive audition (and interoceptive pain somatosensation (Dang-Vu, Schabus, Boly, et al., 2008; Landis et al., 2004; Pivik, Joncas, & Busby, 1999). ROIs were generated in bilateral primary auditory cortex (Heschl's Gyrus) (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008) and bilateral anterior and posterior insula cortices (Schabus, Dang-Vu, et al., 2007), respectively. Finally, ROIs in the hippocampus were constructed based on growing evidence for the role of sleep spindles in episodic memory processing (Diekelmann & Born, 2010), as well as the occurrence of BOLD fMRI hippocampal activity occurring during fast sleep spindles (Schabus, Dang-Vu, et al., 2007). Two hippocampus ROIs were created: within the bilateral anterior and posterior hippocampus, respectively. Standard atlas-defined segmentations of the hippocampus were separated into anterior and posterior sections along the longitudinal axes at the center-of-mass (Wendelken & Bunge, 2010). These segmentations included only the hippocampus proper, excluding extrahippocampal regions (e.g entorhinal and perirhinal cortices).

## 1.3 Results

### Grey matter volume associations with slow waves

The density of NREM slow waves was significantly, and positively, correlated with grey matter volume in the basal forebrain—a region known regulating homeostatic sleep characteristics including slow wave sleep (Kalinchuk et al., 2010; Modirrousta et al., 2007; Monti, 2011), and itself a know representative marker of homeostatic sleep pressure (Esser et al., 2007) (**Fig. 1.1**; **Table 1.2A**). In contrast to density, the amplitude of slow waves was positively correlated with grey matter volume in medial prefrontal cortex, over which the highest magnitude and individual differences in slow waves are known to be expressed (Carrier et al., 2011; Esser et al., 2007; Fein-

berg, de Bie, et al., 2011; Murphy et al., 2009; Vandewalle et al., 2009; Viola, Archer, et al., 2007). Specifically, grey matter volume in both orbital frontal cortex as well as in middle cingulate cortex were significantly and positively correlated with slow wave amplitude across participants (**Fig 1.4**; **Table 1.1B**). Counter to our predictions (Murphy et al., 2009), no voxels in the insula cortex demonstrated significant relationships with slow wave parameters at the whole-brain level (all voxels $p > 0.001$; all clusters FWE corrected, $p > 0.25$).

Beyond these ROIs, uncorrected whole-brain analyses ($p < 0.001$ at the voxel level) revealed that grey matter volume in the cerebellum, together with select regions in parietal and temporal (including medial temporal) lobes, also accounted for individual differences in slow wave density (**Table 1.3**). Discrete frontal and temporal regions also positively correlated within slow wave amplitude, whereas grey matter in occipital cortex as well as the cerebellum negatively correlated with slow wave amplitude (**Table 1.4**).

Finally, to examine the homology of the electrical source generators, and the structural anatomical correlates, of NREM slow waves, EEG current source density analysis was performed. Offering, cross-methodological convergence, sLORETA analyses revealed neural generators in remarkably similar medial frontal regions (**Fig. 1.2**); areas consistent with previous source analyses of slow waves (Murphy et al., 2009). Such descriptive homology between structural (grey matter volume) and functional (EEG source analysis) measures indicates that frontal brain morphology that is associated with slow wave expression converges with frontal brain source generators of the same slow wave EEG expression.

## Grey Matter volume associations with sleep spindle frequency

Contrary to our first prediction, no voxels in the thalamus demonstrated a significant relationship between grey matter volume and sleep spindle frequency, in either the slower (negative correlation) or faster (positive correlation) direction (all voxels $p > 0.001$; all clusters FWE corrected, $p > 0.2$).

However, grey matter volume in exteroceptive and interoceptive sensory cortical ROIs did significantly, and negatively, correlate with sleep spindle frequency. Specifically, greater grey matter volume in both bilateral auditory cortices (Heschl's Gyrus; **Fig. 1.3**), as well as anterior and posterior regions of bilateral insula cortex were predictive of slower sleep spindle frequencies (**Fig. 1.3** and **Table 1.2C**), on average. Interestingly, and further compatible with a sleep protection hypothesis (Dang-Vu, Schabus, Boly, et al., 2008; De Gennaro & Ferrara, 2003; Landis et al., 2004), this same sleep spindle metric explained inter-individual differences in both sleep efficiency ($r^2 = 0.22$, $p = 0.027$; those with slower frequency spindles experienced fewer awakenings during the night), and less time spent awake after sleep onset (WASO; a metric of sleep stability), albeit non-significantly ($r^2 = 0.21$, $p = 0.06$). Beyond our *a priori* regions, initial uncorrected whole brain ($p < 0.001$ at the voxel level) analyses further revealed grey matter associations with slower frequency spindle activity within select frontal and temporal cortex regions (**Table 1.5**).

Conversely, significant and bilateral positive associations were identified with grey matter volume in the hippocampus and sleep spindle frequency, specifically within posterior regions of the hippocampal complex (**Fig. 1.4**; **Table 1D**). Greater grey matter volume in this area was asso-

ciated with faster sleep spindle frequency, across individuals. This positive association between greater grey matter in the hippocampus and sleep spindle frequency was exclusive, with no other regions approaching significance, even at the more liberal statistical threshold of the whole-brain analyses ($p < 0.001$ at the voxel level).

## 1.4 Conclusions

Taken together, these findings demonstrate that inter-individual differences in sleep EEG features are correlated with regional differences of grey matter volume in the human brain, highlighting the notion that structural brain morphology is significantly associated with the qualitative and quantitative expression of human sleep physiology. In the following sections, we discuss possible functional implications and interpretations of these associations for each sleep oscillatory property separately.

### Structural brain correlates of slow waves

When examining the structural predictors of slow wave variability, the identification of correlates within the basal forebrain, offers strong insight into the role of sleep spindles in sleep homeostatic regulation. The basal forebrain forms a major part of the adenosinergic circuitry that supports homeostatic sleep-wake regulation (Kalinchuk et al., 2010; Modirrousta et al., 2007; Monti, 2011). This homeostatic sleep process is manifest in the cortical EEG by way of slow wave activity (Esser et al., 2007), responding in a proportional manner to sleep need (Dijk, Hayes, & Czeisler, 1993; Esser et al., 2007). While varying considerably between individuals, levels of slow wave expression under rested conditions are highly consistent within individuals (Tucker, Dinges, & Van Dongen, 2007), potentially influenced by genotypic variations (Viola, Archer, et al., 2007). We demonstrate that brain structure affords one explanatory factor of inter-individual variance in slow waves, which itself may be determined by genotypic influence. Specifically, grey matter volume in the basal forebrain accounted for nearly 50% of the inter-individual variability in slow wave density; a finding anatomically consistent with the marked disruption of slow waves and their regulation that occurs following lesions to this region (Lai et al., 1999). One testable prediction emerging from these findings is that grey matter integrity of the basal forebrain should serve as a predictor of inter-individual variability in homeostatic sleep regulation, indexed by slow waves, and perhaps most powerfully in response to the condition of sleep deprivation (Dijk et al., 1993). Such biomarkers may offer assistance in clinical conditions where sleep-wake regulation are disrupted, and significant functional impairments emerge (e.g. (Radulescu et al., 2013)).

Beyond density, slow waves have a known frontal-dominant topography of amplitude on the scalp (Kurth et al., 2010; Riedner et al., 2007). Consistent with that topography, we identified that grey matter volume within select midline prefrontal regions of the anterior cingulate and orbital frontal cortex positively correlated with slow wave amplitude. Offering convergent evidence, homologous medial prefrontal regions (peak source activity in the cingulate cortex) were identified using EEG source analysis of slow wave peak oscillations; similar to previous EEG source

analysis of slow waves (Murphy et al., 2009). While remaining tentative, such convergence across reports increasingly supports the midline frontal cortex as critical in the determination of NREM slow wave EEG generation. More broadly, the association between slow waves and regions of medial frontal cortex is consistent with ontogenetic differences in slow wave activity across the lifespan, since both frontal cortex grey matter and slow waves express congruent developmental alterations early in life (Kurth et al., 2010) and pernicious reductions later in life (Carrier et al., 2011).

While the insula cortex was a target region potentially accounting for inter-individual differences in slow waves, based on previous EEG source analysis (Murphy et al., 2009), no associations were identified for insula cortex were identified, for either metric of NREM slow waves. While the insula cortex may be involved in the generation of slow waves (Murphy et al., 2009), grey matter volume of the insula, in this study, does not appear to modulate the expression of those waves across individuals.

For slow wave density, two additional regions of relevance were observed from the whole brain results. First, grey matter volume in parahippocampal gyrus also was associated with differences in the density of slow waves, offering homologous anatomical regions to those demonstrated as active during the coincidence of (rather than individual differences in) slow waves, visualized using fMRI (Dang-Vu, Schabus, Desseilles, Albouy, et al., 2008). The identification of the parahippocampal gyrus in these results underscores the proposed role of slow waves—in addition to, or in conjunction with, sleep spindles—in supporting episodic memory processes (Abel et al., 2013). Second, grey matter volume in a number of sub-areas within the cerebellum further demonstrated a positive relationship with slow wave density. While unexpected as slow waves derive from primary cortical sources (Murphy et al., 2009), it is of note that the incidence of slow waves in the EEG co-occurs with fMRI BOLD signal increases in similar cerebellar regions (Dang-Vu et al., 2008b) as well. The contribution of the cerebellum to determining sleep EEG—especially considering the role of sleep in motor learning (Robertson, 2009)—warrants further investigation.

## Structural brain correlates of sleep spindle frequency

Consistent with theories of sleep protection against exogenous and endogenous conscious perception (De Gennaro & Ferrara, 2003), grey matter volume in auditory and insular cortices negatively correlated with sleep spindle frequency, predictive of slower sleep spindles across individuals. These associations between slower sleep spindle frequency and greater grey matter volume in sensory areas may reflect the role of sleep spindles (of slower frequency) in the protection from sensory disruption (both exteroceptive, and interoceptive) during sleep. Indeed, focusing on audition as the prime exogenous route of sensory sleep interference, recent findings have demonstrated that inter-individual variability in sleep spindles over sensory cortex predicts the extent to which the sleep state is protected and hence conserved in response to experimental auditory stimulation (Dang-Vu, Schabus, Boly, et al., 2008). Circumstances of acquired hearing loss have further been associated with decreases in auditory grey matter and congruent reductions in slow-frequency spindles (Landgrebe et al., 2009; Scrofani et al., 1996). These associations between slower sleep spindle frequency and grey matter volume in sensory areas may reflect the role of

slower frequency sleep spindles in the protection from sensory disruption (both extereoceptive, and intereoceptive) during sleep.

Beyond exogenous (auditory) stimuli, endogenous sensory information, most notably pain, is similarly recognized to markedly disrupt sleep (Buenaver & Smith, 2007). Chronic pain has been associated independently with decreases in the number of sleep spindles (Landis et al., 2004) and reductions in insula cortex integrity (Kim et al., 2008). While remaining speculative, the association between grey matter volume in insula cortex sleep spindle frequency in the current study provides a basis on which these previously independent findings in chronic pain may be united. The loss of insular grey matter in chronic pain may represent one putative mechanism that leads to decreases in slow sleep spindle activity, and with it, the susceptibility to interoceptive pain sensation during sleep (Buenaver & Smith, 2007); a proposal that can be empirically tested in future studies. Although the insula is involved in processes other than pain perception, the reported loss of insular grey matter in chronic pain may represent one putative mechanism, to mediate a reduction in slow sleep spindle activity, and with it, increased susceptibility to interoceptive pain sensation during sleep (Buenaver & Smith, 2007). While this model remains speculative, future patient-cohort studies employing structural MRI, in conjunction with quantitative sensory testing, and sleep EEG recordings will be able to further elucidate such a mechanism.

In contrast to slower spindles, faster frequency sleep spindles (commonly in the range of 13–15 Hz) continue to be implicated in hippocampal-dependent memory processing (Diekelmann & Born, 2010). For example, inter-individual differences in sleep spindles, including fast sleep spindles, are associated with the benefit of prior sleep on subsequent hippocampal encoding ability (Mander, Santhanam, et al., 2011), and sleep after learning in the offline consolidation of episodic memory (Gais, Mölle, Helms, & Born, 2002; Rauchs et al., 2008; Saletin et al., 2011; Schabus, Gruber, et al., 2004; Schabus, Hoedlmoser, et al., 2008). Likewise fMRI-identified functional activity in the hippocampus coinciding with sleep spindles has been related to learning and memory processes (Andrade et al., 2011; Bergmann, Mölle, Diedrichs, Born, & Siebner, 2012). Offering unique structural evidence, we demonstrated that hippocampal grey matter volume was exclusively positively correlated with spindle frequency across individuals. While no memory tasks were included in the present study to test the functional outcome of this association, the significant relationship between hippocampus grey matter volume and faster spindle frequency is consistent with a broad collection of pathological circumstances describing not only marked impairments in sleep spindle activity, but co-occurring deficits in hippocampal grey matter and episodic memory, including Alzheimer's disease, Schizophrenia as well as sleep apnea (Barnes et al., 2009; Ferrarelli et al., 2007; Hedden & Gabrieli, 2004; Himanen, Virkkala, Huupponen, & Hasan, 2003; Joo, Tae, Lee, et al., 2010; Kloepfer et al., 2009; Rauchs et al., 2008; Tamminga, Stan, & Wagner, 2010). Our findings offer a foundation on which these coinciding features may be considered interrelated, suggesting a testable link between deficits in hippocampal structure, impoverished sleep spindle activity, memory impairment. Recent evidence from healthy aging demonstrates that age-related deficits in hippocampal-dependent memory encoding is associated both with a decrease in fast spindle activity, but moreover with macroscopic changes in hippocampus structure (Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013). Similar studies are called for both in young healthy adults, as well as early in life, as well as within the patient

populations described above. Such work will be able to examine the potential causal pathway between hippocampal integrity, spindle activity and memory function across both the lifespan and disease.

In addition to our *a priori* regions of interest, several additional areas emerged that were negatively correlated with spindle frequency, at the whole-brain level. These included select frontal lobe areas, most prominent in bilateral dorsolateral prefrontal cortex. This latter associations is of potential note given both the known frontal-dominant EEG surface expression of slow sleep spindles (De Gennaro & Ferrara, 2003; Schabus, Dang-Vu, et al., 2007), and a recent report of congruent lateral prefrontal cortex fMRI BOLD activity associated with sleep spindle occurrence (Schabus, Dang-Vu, et al., 2007). While grey matter associations with primary sensory and perceptual areas are consistent with a potential protective function of spindles, a role for human dorsolateral prefrontal cortex in sensory gating has recently been advanced (Mayer et al., 2009). Within this context, our findings offer tentative support to a framework where primary sensory and perceptual areas (here, auditory and insula cortex), in cooperation with high-order rating networks in dorsolateral prefrontal cortex, may form sleep spindle regulating anatomical networks capable of gating sensory interference and hence maintain the sleep state.

Contrary to the original hypothesis, no significant associations were identified between sleep spindle activity and thalamic grey matter. One potential explanation for this lack of association is that the thalamus is not well segmented by T1-weighted structural MRI, limiting the possibility of identifying such thalamic relationships (Eggert, Sommer, Jansen, Kircher, & Konrad, 2012). Alternatively, even with accurate segmentation, the absence of an association in the present data does not challenge the established role of the thalamus in generating spindles (Steriade, Deschênes, et al., 1985). Instead, our results may be interpreted in the context of quantity relative to quality. While thalamic processes are critical for the instigation of sleep spindle events (quantity) (Roth, Jeanmonod, Magnin, Morel, & Achermann, 2000; Steriade, Deschênes, et al., 1985), the EEG expression of qualitative features of spindles (e.g. individual frequency) may be less dependent on thalamic structure and more dependent on down-stream cortical connections that determine spindle function. This interpretation is consistent with previous attempts to source analyze EEG sleep spindle demonstrating differential cortical (rather than thalamic) source associations of fast and slow sleep spindles (Ventouras et al., 2007).

## Future directions

The current data propose that the expression of sleep EEG is directly related to variability in brain morphology between individuals. However, this study does not indicate whether measurable functional consequences (e.g. learning and memory) emerge from these relationships. Recent data in late-life adults, for example, suggest that age-related cognitive deficits in learning and memory result from changes in sleep EEG due to regional brain atrophy (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013), consistent with the relationships presented here. Specifically, age-related atrophy in prefrontal grey matter led to concomitant changes in slow wave activity (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013) and with it memory consolidation. Similar findings were demonstrated with hippocampal grey

matter and memory encoding in this cohort (Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013). These studies suggest that the relationships described in young adults here would also be predictive of functional consequences (e.g. greater hippocampus grey matter leading to faster sleep spindles, and associated hippocampus-dependent processing of memories during sleep). While no study has yet to directly measure these associations in healthy young adults, further studies, expanding on the current work by including learning and memory outcome measures, will be able to determine the functional consequences of these structural-EEG relationships.

In the context of sleep and brain structure across the lifespan, it is important to note that both the aging studies described above, as well as those in adolescents (Buchmann et al., 2010) are cross-sectional in nature. It is not known whether young- and old-age related alterations in brain structure causally precede, or only co-occur with, changes in NREM sleep physiology and associated cognitive performance. Future prospective longitudinal studies will serve to disentangle this complex system of relationships. Understanding whether these relationships are causal or simply co-occurring has fundamental translational significance in understanding the mechanisms underlying changes in sleep-dependent cognition in clinical cases (e.g. obstructive sleep apnea, narcolepsy, insomnia) where brain structure abnormalities emerge (Benson et al., 1996; Joo, Tae, Lee, et al., 2010; Macey et al., 2002; O'Donoghue et al., 2005; van Kammen, van Kammen, Peters, Goetz, & Neylan, 1988; Wiegand, Moller, Schreiber, Lauer, & Krieg, 1991). Should brain structure directly precede, cognitive impairments and sleep abnormalities in these populations—or across ontogeny—the specific regional relationships (e.g. prefrontal grey matter - slow wave activity) in this study may serve as early biomarkers for cognitive impairment throughout the lifespan.

## 1.5 Tables

Table 1.1: Group sleep statistics

| | Mean ± s.e. |
|---|---|
| Sleep Continuity | |
| Total Dark Time (min.) | $482.80 \pm 1.75$ |
| Total Sleep Time (min.) | $436.84 \pm 5.53$ |
| Sleep Efficiency (%) | $90.50 \pm 1.16$ |
| Latency to Sleep Onset (min.) | $18.32 \pm 3.30$ |
| Latency to REM Sleep (min.) | $103.05 \pm 12.25$ |
| Wake After Sleep Onset (min.) | $22.57 \pm 5.11$ |
| Sleep Architecture | |
| Stage 1 (% TST) | $5.06 \pm 0.56$ |
| Stage 2 (% TST) | $52.07 \pm 1.43$ |
| Stage 3 (% TST) | $10.03 \pm 0.49$ |
| Stage 4 (% TST) | $12.87 \pm 1.42$ |
| Slow Wave Sleep (% TST) | $22.90 \pm 1.52$ |
| REM Sleep (% TST) | $19.97 \pm 1.12$ |

Sleep Stages presented as % of Total Sleep Time. Slow Wave Sleep (Stages 3&4 NREM).

Table 1.2: Grey matter volume correlates of sleep spindle frequency and slow waves (*a priori* regions)

| Anatomical Cluster | | Local Maxima | | | $z_{Peak}$ | $p_{SVC-Cluster}$ | $p_{SVC-Peak}$ |
|---|---|---|---|---|---|---|---|
| | | $x$ | $y$ | $z$ | | | |
| **A. Grey matter volume positively correlating with slow wave density** | | | | | | | |
| L | BF/Hypothalamus | $-2$ | 2 | $-8$ | 3.46 | 0.008 | 0.008 |
| R | | 8 | 3 | $-5$ | 3.16 | | 0.018 |
| **B. Grey matter volume positively correlating With slow wave amplitude** | | | | | | | |
| R | Orbital Frontal Cortex | 2 | 34 | $-27$ | 4.53 | 0.020 | 0.001 |
| L | | $-1$ | 34 | $-27$ | 3.87 | 0.018 | 0.008 |
| R | Cingulate Cortex | 7 | $-9$ | 32 | 3.62 | 0.035 | 0.036 |
| | | 8 | $-17$ | 33 | 3.33 | | 0.078 |
| **C. Grey matter volume negatively correlating with sleep spindle frequency** | | | | | | | |
| L | Posterior Insula | $-40$ | $-26$ | 15 | 4.33 | 0.011 | 0.014 |
| L | Heschl's Transverse Gyrus | $-39$ | $-26$ | 14 | 3.58 | 0.008 | 0.005 |
| R | | 52 | $-19$ | 8 | 3.72 | 0.020 | 0.016 |
| | | 54 | $-15$ | 7 | 3.56 | 0.022 | 0.022 |
| L | Anterior Insula | $-35$ | $-21$ | 8 | 3.48 | 0.021 | 0.019 |
| | | $-46$ | $-5$ | 14 | 3.62 | 0.050 | 0.047 |
| R | | 38 | 21 | 2 | 3.43 | 0.033 | 0.021 |
| **D. Grey matter volume positively correlating sleep spindle frequency** | | | | | | | |
| L | Posterior Hippocampus | $-25$ | $-27$ | $-8$ | 3.52 | 0.015 | 0.009 |
| R | | 26 | $-31$ | $-9$ | 3.64 | 0.016 | 0.006 |

Cluster statistics using non-stationary correction. SVC $p$-values represent FWE correction.

Table 1.3: Grey matter volume correlating with slow wave density (uncorrected $p$<0.001, extent: 30 voxels)

| Anatomical Cluster | | Local Maxima | | | $z_{Peak}$ | Cluster Size |
|---|---|---|---|---|---|---|
| | | $x$ | $y$ | $z$ | | |
| **A. Grey matter volume positively correlating with slow wave density** | | | | | | |
| R | Middle Occipital Gyrus | 35 | −80 | 18 | 4.36 | 2685 |
| L | Cerebellum (Crus I) | −34 | −79 | −18 | 3.98 | 1656 |
| | | −20 | −83 | −19 | 3.24 | |
| L | Cerebellum | −5 | −41 | −9 | 3.91 | 752 |
| R | Vermis | 4 | −68 | −28 | 3.62 | 2249 |
| | | −17 | −70 | −39 | 3.52 | |
| | | −8 | −73 | −31 | 3.46 | |
| R | Postcentral Gyrus | 16 | −36 | 57 | 3.58 | 967 |
| L | Cerebellum (Crus I) | −50 | −53 | −32 | 3.52 | 387 |
| R | Cerebellum (Crus I) | 46 | −66 | −21 | 3.47 | 578 |
| L | Postcentral Gyrus | −16 | −27 | 59 | 3.46 | 37 |
| L | Inferior Temporal Gyrus | −47 | −53 | −6 | 3.45 | 330 |
| R | Parhippocampal Gyrus | 16 | −14 | −35 | 3.44 | 43 |
| R | Fusiform Gyrus | 24 | −8 | −49 | 3.38 | 348 |
| R | Postcentral Gyrus | 40 | −37 | 59 | 3.36 | 277 |
| L | Parahippocampal Gyrus | −17 | −12 | −38 | 3.34 | 71 |
| R | Inferior Temporal Gyrus | 44 | −64 | −10 | 3.33 | 340 |
| R | Cuneus | 6 | −93 | 24 | 3.31 | 74 |
| **B. Grey matter volume negatively correlating with slow wave density** | | | | | | |
| R | Supramarginal Gyrus | 50 | −39 | 25 | 3.77 | 824 |

Cluster size using non-stationary correction.

Table 1.4: Grey matter volume correlating with slow wave amplitude (uncorrected $p$<0.001, extent: 30 voxels)

| Anatomical Cluster | | Local Maxima | | | $z_{Peak}$ | Cluster Size |
|---|---|---|---|---|---|---|
| | | $x$ | $y$ | $z$ | | |
| **A. Grey matter volume positively correlating With slow wave amplitude** | | | | | | |
| R | Superior Frontal Gyrus | 29 | 4 | 64 | 3.57 | 526 |
| L | Precentral Gyrus | −52 | 1 | 38 | 3.56 | 632 |
| R | Middle Temporal Gyrus | 44 | −1 | −21 | 3.52 | 318 |
| L | Middle Frontal Gyrus | −44 | 46 | 24 | 3.47 | 115 |
| R | Superior Frontal Gyrus | 18 | 0 | 58 | 3.35 | 114 |
| **B. Grey matter volume negatively correlating with slow wave amplitude** | | | | | | |
| R | Fusiform Gyrus | 35 | −63 | −11 | 3.7 | 656 |
| L | Cerebellum | −5 | −46 | −2 | 3.33 | 86 |
| L | Cerebellum | −12 | −45 | −63 | 3.22 | 36 |
| R | Inferior Occipital Gyrus | 44 | −80 | −14 | 3.13 | 42 |

Cluster size using non-stationary correction.

Table 1.5: Grey matter volume correlating with sleep spindle frequency (uncorrected $p$<0.001, extent: 30 voxels)

| Anatomical Cluster | | Local Maxima | | | $z_{Peak}$ | Cluster Size |
|---|---|---|---|---|---|---|
| | | $x$ | $y$ | $z$ | | |
| **Grey matter volume negatively correlating with sleep spindle frequency** | | | | | | |
| R | Superior Temporal Gyrus | 58 | −18 | 7 | 4.47 | 1446 |
| L | Middle Frontal Gyrus | −32 | 53 | 18 | 3.95 | 2479 |
| | | −35 | 45 | 24 | 3.23 | |
| R | Middle Frontal Gyrus | 35 | 52 | 7 | 3.76 | 1538 |
| L | Lingual Gyrus | −16 | −80 | 2 | 3.60 | 120 |
| R | Cerebellum | 20 | −57 | −66 | 3.46 | 173 |
| | | 14 | −66 | −64 | 3.46 | |
| R | Supramarginal Gyrus | 53 | −37 | 32 | 3.45 | 297 |
| L | Postcentral Gyrus | −46 | −29 | 49 | 3.44 | 396 |
| R | Supplemental Motor Area | 10 | 21 | 52 | 3.39 | 179 |
| L | Middle Frontal Gyrus | −33 | 49 | 32 | 3.29 | 91 |
| L | Rolandic Operculum | −48 | −4 | 14 | 3.26 | 70 |
| R | Gyrus Rectus | 8 | 50 | −15 | 3.21 | 43 |
| R | Inferior Temporal Gyrus | 41 | −4 | 39 | 3.21 | 146 |
| L | Superior Orbital Gyrus | −11 | 62 | −14 | 3.16 | 37 |
| R | Superior Occipital Cortex | 20 | −80 | 42 | 3.15 | 35 |

Cluster size using non-stationary correction.

## 1.6 Figures

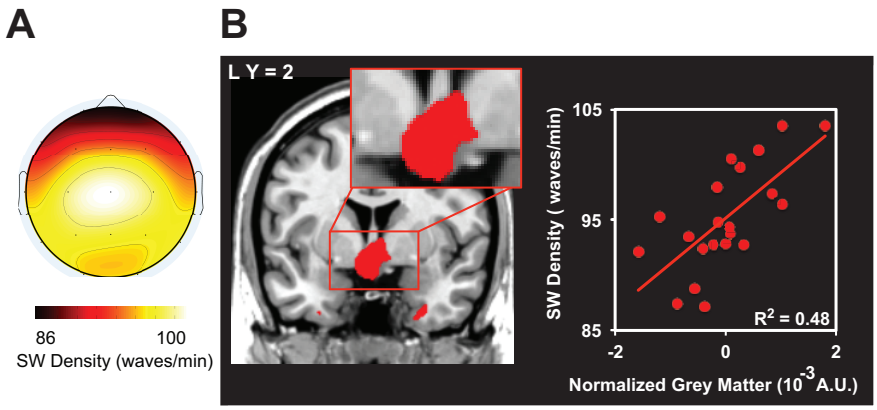


Figure 1.1: Grey matter volume (GM) associations with NREM slow wave density within *a priori* regions of interest.

(a) (left) topographic plot of EEG slow wave (SW) density, demonstrating centro-parietal surface distribution, followed by (b) (middle, right) positive association between SW density and GM in the basal forebrain / hypothalamus (coronal), followed by a scatterplot relating grey matter and SW density at the peak voxel of basal forebrain / hypothalamic cluster. Image at MNI [x y z]: [-2 2 -8]. Statistical maps are displayed at $p < 0.005$.

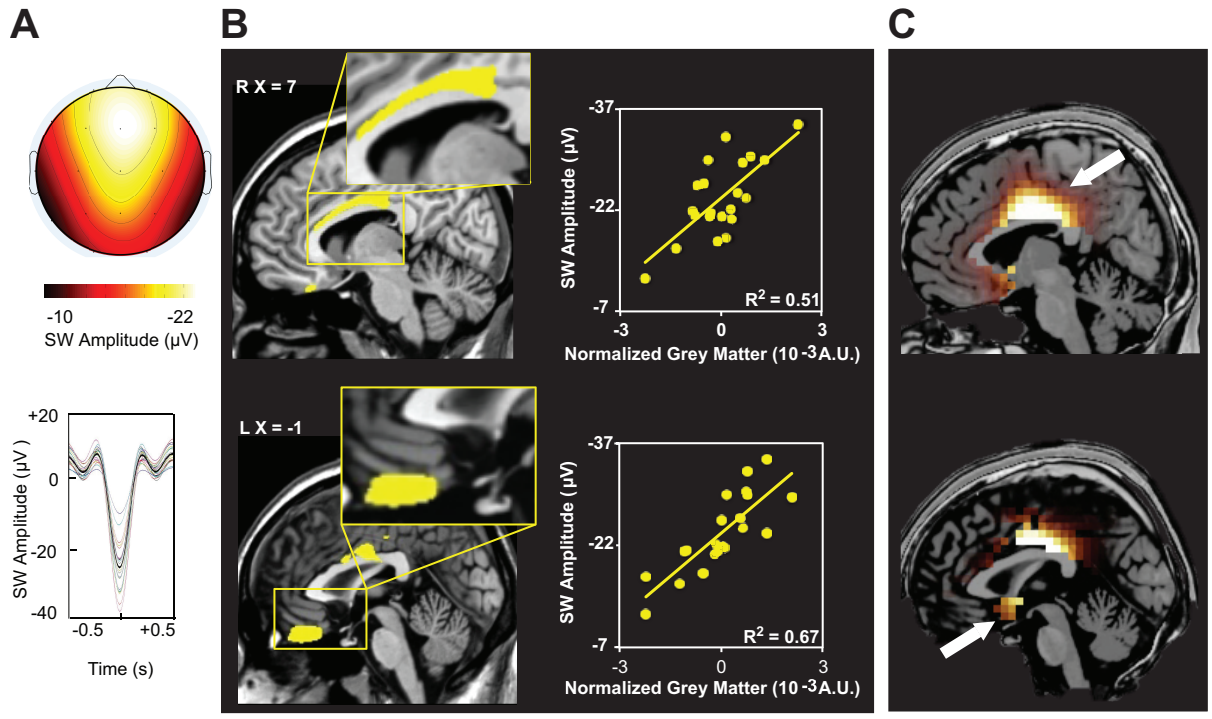


Figure 1.2: Grey matter volume (GM) associations with NREM slow wave amplitude within *a priori* regions of interest.

(a) (left) topographic plot of EEG slow wave peak amplitude, demonstrating canonical frontal dominant surface distribution, with the corresponding average SW oscillation at electrode derivation Fz plotted for each subject (bold group average), (b) (middle) positive association between SW amplitude and GM in middle cingulate and mesial orbital frontal cortex, each with strongly convergent anatomical findings (right) from sLORETA electrical source analyses of the peak SW amplitude, followed by scatterplot relating grey matter and SW amplitude at the peak voxels of the cingulate and orbital frontal clusters, respectively. Arrows designate similarity between GM correlates and source-generators of slow waves. Top image at MNI [x y z]: [7 -9 32], bottom image at MNI [x y z]: [-1 34 -27]. Statistical maps are displayed at $p < 0.005$.

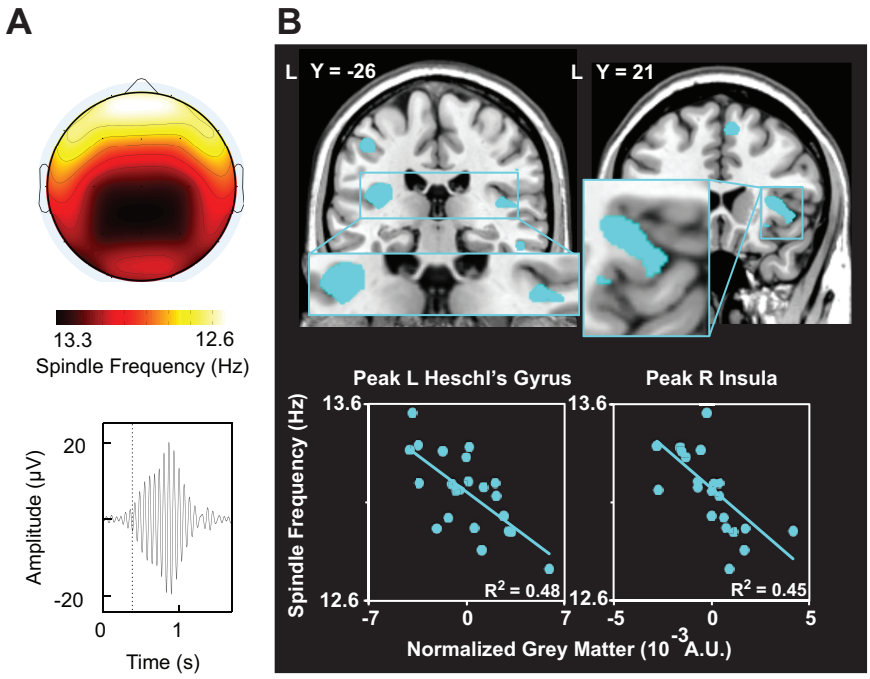


Figure 1.3: Grey matter volume (GM) associations with slower sleep spindles within *a priori* regions of interest.

(a) (left) topographic plot of frontal dominant slower spindle frequency, with representative sleep spindle at electrode derivation Cz. (b) (right) associations between slower sleep spindle frequencies and GM in bilateral auditory cortex (Heschl's Gyrus) and in the left and right anterior and posterior insula, respectively, followed by scatterplots relating grey matter and spindle frequency at the peak voxels of the left Heschl's Gyrus and right anterior cingulate clusters, respectively. Left image at MNI [x y z]: [-39 -26 14], Right image at MNI: [38 21 2]. Statistical maps are displayed at $p < 0.005$.

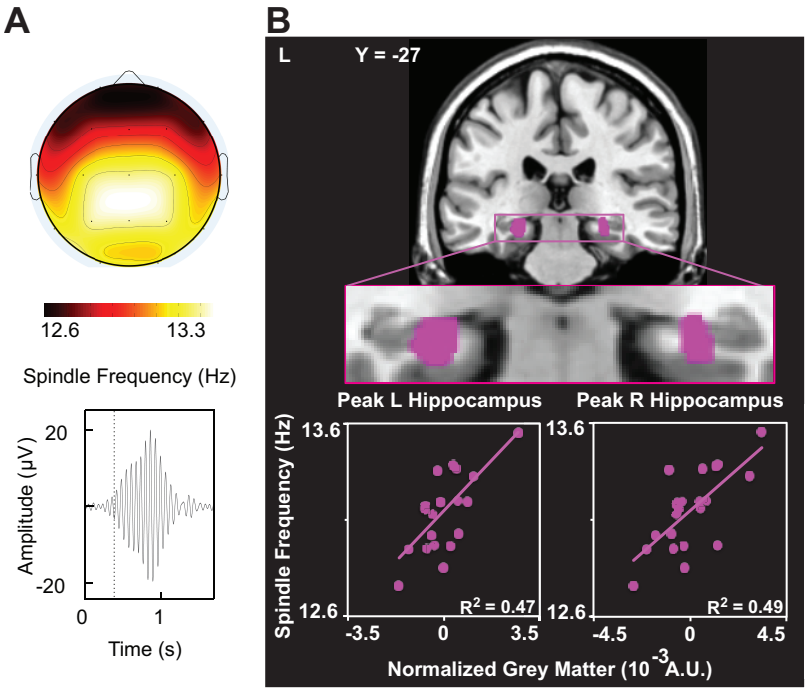


Figure 1.4: Grey matter volume (GM) associations with faster sleep spindles within *a priori* regions of interest.

(a) (left) topographic plot of posterior dominant faster sleep spindle frequency. (b) (right) positive association between faster sleep spindle frequencies and GM in bilateral posterior hippocampus, followed by scatterplots relating grey matter and spindle frequency at the peak voxels of the left and right hippocampus clusters, respectively. Image at MNI [x y z]: [-25 -27 -8]. Statistical maps are displayed at $p < 0.005$.

# Chapter 2

# Human hippocampal sub-structure predicts vulnerability to memory impairment following sleep deprivation and subsequent recovery by NREM slow waves

While hippocampus-dependent memory functioning is impaired by sleep deprivation, the factors accounting for this impairment remain largely unknown, as does the possibility that such memory function can be restored by recovery sleep. Combining high-density EEG and high resolution MRI, this study demonstrates that the structural morphology of the human hippocampus, and specifically the CA3/Dendate Gyrus (DG) subfield, represents one factor explaining inter-individual variability in impairment vulnerability to the effects of sleep loss. Further, statistical path analyses revealed that CA3/DG subfield morphology causally accounts for the magnitude of homeostatic response of NREM slow wave activity during recovery sleep, which, in turn, predicts the restoration of post-sleep learning ability. Such findings suggest that the macroscopic sub-structure of the human hippocampus represents one novel morphological factor governing inter-individual differences in both the severity of learning impairment caused by sleep deprivation, and the restoration of such mnemonic function following recovery NREM sleep. Moreover, such findings offer translational significance by offering one interacting framework in disorders where sleep disruption, memory impairments and hippocampal abnormalities are highly co-morbid.

## 2.1 Introduction

Sleep deprivation, particularly of non-rapid eye movement (NREM) sleep, impairs the capacity of the human hippocampus to encode new episodic memories (Yoo et al., 2007; Van Der Werf et al., 2009). In contrast, the presence of NREM sleep and its associated oscillations promotes the restoration of hippocampal-dependent encoding (Mander, Santhanam, et al., 2011; Antonenko et al., 2013). Nevertheless, marked variability exists in the degree to which both sleep deprivation and recovery sleep affect such learning ability (Yoo et al., 2007), the underlying mechanism(s) of which remain unknown. This study examines two candidate interacting factors: hippocampal structural morphology, and recovery NREM sleep physiology. Three lines of evidence mutually support this hypothesis.

First, the structure of the brain is a known determinant of its function. For example, the severity of hippocampal damage predictive of cognitive impairment in cases of neural insult (Fogelson et al., 2009), late-life aging (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013), and dementia (Nho et al., 2012) . Moreover, inter-individual differences in the volume of the hippocampus—including hippocampus subfield regions of CA3/Dendate Gyrus (CA3/DG) (Tamminga et al., 2010)—is known to explain variability in learning ability (2). Despite these rested relationships, no study has yet to examine whether the same structural properties of hippocampus subfields predict the severity of learning impairment under conditions of sleep deprivation, or the restoration of learning following recovery sleep.

Second, sleep deprivation is known to selectively impact hippocampal function in humans, indexed using fMRI, associated with significant learning deficits (Yoo et al., 2007; Van Der Werf et al., 2009). Moreover, rodent studies describe that selective hippocampus subfields—especially the CA3/DG subregion—suffer marked disruption of the cellular and molecular mechanisms governing plasticity under conditions of sleep deprivation (Abel et al., 2013). These dysfunctions have been observed in measures of long-term potentiation (Vecsey et al., 2009), as well as in neurogenesis (Guzman-Marin, Bashir, Suntsova, Szymusiak, & McGinty, 2007), the latter occurring especially in CA3/DG, both of which results in learning impairments (Abel et al., 2013).

Finally, sleep loss impairments of hippocampal function and learning appear to be preferentially due to the loss of NREM slow waves, evidence by selective deprivation paradigms (Van Der Werf et al., 2009). Further, NREM slow waves are known to correlate with the restoration of learning ability and associated plasticity (Antonenko et al., 2013), with NREM slow waves themselves responding in a homeostatic manner during recovery sleep that is proportional to the extent of accumulated sleep loss (Aeschbach & Borbély, 1993). As such, they have been used as an index of use-dependent recovery brain function in the context of sleep deprivation (Banks, Van Dongen, Maislin, & Dinges, 2010).

Despite these findings, it currently remains unknown whether the morphology of human hippocampal subfields represent one novel structural factor explaining inter-individual differences in the magnitude of learning impairment caused by sleep deprivation, and the success of functional memory restoration following recovery NREM sleep.

Targeting this issue, the current study aims to test the following hypothesis: that hippocampal brain structure, and NREM oscillatory physiology, may respectively determine inter-individual

difference in (1) mnemonic vulnerability (or converse resilience) to the impact of sleep deprivation, and (2) the subsequent restorative benefits of recovery sleep.

## 2.2 Materials and Methods

### Participants

15 healthy adults (19.6 ± 1.45yrs, 7-males) completed a repeated-measures crossover design. Participants abstained from caffeine and alcohol for the 72 hours before and during the entire course of the study and kept a normal sleep-wake rhythm (7–9 hours of sleep per night with sleep onset before 01:00 in the morning and rise time no later than 09:00) for the 3 nights prior to the study participation, as verified by sleep logs and actigraphy (a wristwatch movement sensor, sensitive to wake and sleep states). Exclusion criteria, assessed using a prescreening questionnaire, were: a history of sleep disorders, neurologic disorders, closed head injury, Axis I psychiatric disorders according to the DSM-IV criteria (encompassing mental disorders including depression, anxiety disorders, bipolar disorder, attention deficit disorder and schizophrenia), history of drug abuse and current use of anti-depressant or hypnotic medication. Subjects who reported drinking 3 or more caffeine-containing substances a day such as coffee, tea or caffeine containing soft drinks, were exclude from the study. The study was approved by the local human studies committee, with all participants providing written informed consent.

The study consisted of a crossover repeated-measures design involving three conditions: (1) sleep rested (following a full night of sleep), (2) sleep deprived (approximately 24 hours total sleep deprivation), and (3) sleep recovery using a 90-minute nap opportunity, monitored with high-density sleep electroencephalagraphy (hdEEG). Each participant completed the entirety of the protocol. The order three conditions were pseudo-counterbalanced between individuals. As such that participants either first completed the sleep rested session and returned after a week-delay for the sleep deprived and sleep recovered sessions, or completed the deprivation and recovery sessions first, returning a week later for the sleep rested session. The order of the sleep deprived and sleep recovery sessions was fixed due to the requirements of sleep recovery following sleep deprivation.

### Behavioral pattern separation

To index learning ability during each of the three conditions, participants performed a validated behavioral pattern separation learning task (Yassa & Stark, 2011). Pattern separation—the ability of the hippocampus to hold highly similar, yet distinct, memories as separate rather then conflicting representations (O'Reilly & Norman, 2002)—is particularly dependent upon the CA3/DG region (3) mentioned above. Three task versions (each with unique stimuli) were used in the current study, with each version presented in a counterbalanced order, with regards to sleep condition, across individuals.

The behavioral pattern separation task extends upon a traditional continuous recognition paradigm (Donaldson, et al., 1968). In short, nameable objects are displayed twice in a continuous stimuli stream. Participants are required to endorse the image as new upon first viewing (encoding trial), old upon second viewing (recognition trial). All stimuli were presented using the Psychtoolbox toolkit (http://psychtoolbox.org/) within the MATLAB computing environment (Mathworks, Natick, MA). This task has been used previously (Kirwan & Stark, 2007) to study pattern separation both behavioraly (Kirwan & Stark, 2007) as well as in concert with hippocampus subfield fMRI (Kirwan & Stark, 2007; Bakker, Kirwan, Miller, & Stark, 2008).

480 images in total were presented in a pseudo-randomized order for 2.5 seconds at a time spread across 6 runs. 96 images ("repeated pairs") were shown twice, once for initial encoding, and once for later retrieval. Another 96 images ("similar pairs") were shown once, followed by a later presentation of a highly similar, yet unique lure image (see **Fig. 2.1** for example stimuli). Finally, an additional 96 foil images were presented a single time, with neither an identical nor similar lure repeat later in the task. The length of time between the first presentation of a pair, and its later re-presentation (regardless of trial type) varied between 10 and 40 trails (30 and 120 seconds) randomly to ensure that working memory was not responsible for successful behavioral responses (Kirwan & Stark, 2007).

Upon seeing each image participants were asked to, by a keyboard press, indicate whether the image is one they have seen before (an "old'' response), one that is similar to one they have seen before (a "similar'' response), or one that they have never seen before (a "new'' response). The primary memory outcome measure used was the validated separation bias index (Yassa & Stark, 2011), derived as the difference between the proportion of similar lures correctly identified as "similar" (p("similar" | similar)) and the proportion of repeated images incorrectly identified as "similar" (p("similar" | old)). Higher values of this difference measure represent higher degrees of pattern separation accuracy (Yassa and Stark, 2011), reflecting greater ability to dissociate memory representations that are highly similar. This behavioral metric has been previously linked directly the function of the human CA3/DG hippocampus subfield using high-resolution fMRI (Yassa & Stark, 2011).

## Structural neuroimaging acquisition and analysis

To quantify hippocampus subfield structure, a high-resolution T1-weighted image was acquired for each participant at the time of behavioral testing on a 3T Siemens Trio scanner (256 x 256 matrix; TR=1900; TE = 2.52; flip angle = 9°; FOV 256mm; 1 x 1 x 1mm voxels). From this structural scan, hippocampus structure was examined using a validated diffeomorphic based morphometry technique (DBM) (Chung et al., 2001), sensitive to local morphological shape changes within the hippocampus (Das et al., 2012). DBM was accomplished using the Advanced Normalization Tools (ANTS) normalization toolbox. In short, DBM, circumvents the reliance on intensity-based segmentations typical of volumetry studies by directly analyzing the jacobian resulting from normalization of each individual's structural scan to a high-resolution template image. ANTS employs a diffeomorphic-based approach to image registration with a high degree of precision compared to

common linear, and non-linear registration methods (Klein et al., 2009) and DBM is particularly sensitive to small variations within the hippocampus (Das et al., 2012).

Each participant's T1-weighted scan was first normalized to a validated high-resolution template of hippocampus subfields (Bakker et al., 2008) suitable to this age-population. This template has been used in previous studies to normalize with the desire to ensure highest precision of overlap between medial temporal lobe structures (Bakker et al., 2008; Kirwan, Jones, Miller, & Stark, 2007; Kirwan & Stark, 2007). Following normalization to the template, reverse warping was performed in ANTS to warp the segmented medial temporal lobe regions-of-interest (ROI) labels inversely to each participant's individual scan. These hippocampal segmentations included three subfields within the hippocampus: CA1, Subiculum, and CA3 / Dendate Gyrus (CA3/DG; the dendate gyrus cannot be distinguished from CA3 at standard MRI resolutions (Yassa & Stark, 2011)).

To quantify volume of these subregions, the voxel-wise jacobian values were averaged within each ROI (separately for left and right segmentations before being averaged bilaterally), for each subject, offering an index of volume. To aid in interpretation, values were inverted (multiplied by -1), resulting in negative values corresponding to a smaller segmented volume and positive values indicates a larger segmented volume.

## Polysomnographic monitoring

Each participant completed two session of polysomnographic (PSG) sleep monitoring, both before the rested behavioral session, as well as after sleep deprivation. During the rested condition, participants slept in the laboratory monitored by PSG to ensure that participants were fully-rested the following morning. Specifically PSG was recorded using a Grass Technologies Comet XL system (Astro-Med, Inc., West Warwick, RI). Electroencephalography (EEG) was recorded at 19 standard locations conforming to the International 10-20 System. Sleep staging was performed in accordance with standardized techniques (Rechtschaffen & Kales, 1968). Sleep statistics for both sleep continuity and sleep architecture are reported in **Table 2.1**; revealing normative sleep patterns for this age group (Ohayon et al., 2004) during the night of rested sleep. As such, participants can be interpreted as being fully rested prior to any behavioral testing.

Following sleep deprivation, each participant received a short recovery nap opportunity. During this nap, high-density PSG was recorded using an Electrical Geodesics, Inc. (Eugene, OR) GES 300 amplifier system. This nap used a 128-channel high-density EEG array as part of a larger study examining regional topography of recovery sleep EEG. EOG and EMG were recorded as above, with the exception that EOG was recorded using adapted vertical and horizontal EOG derivations. Data were digitized at 1000 Hz. Identical scoring criterion were used for the recovery nap, focused once again on the C3-A2 electrode derivation. Polysomnographic statistics from this recovery nap are reported in **Table 2.2**. One subject did not contribute a nap recording, due to technical issues. This subject completed the remainder of the study including all behavioral tasks.

## EEG analysis

This study focused *a priori* on the NREM oscillatory activity present during the recovery nap. Nap EEG was processed according to established methods. In short, following sleep scoring, each EEG channel was re-referenced to the average of the left and right mastoids for quantitative signal processing. All EEG analyses were performed in MATLAB 7.5 (The Mathworks, Natick, MA), including the add-in toolbox EEGLAB (http://sccn.ucsd.edu/eeglab/). The current analyses focused solely on the subsection of 19 topographical electrodes representing the 10-20 electrodes also recorded during rested sleep. The EEG was filtered offline (EEGLAB function eegfilt) using Finite Impulse Response (FIR) filters (low-pass at 50Hz, high-pass at 0.6Hz). A high-pass cutoff frequency of 0.6 Hz was chosen to remove possible slow artifact in the EEG. Signals were then visually marked for artifact in 4-second epochs. Each 4-second epoch of data used for artifact-rejection was matched its corresponding scored sleep.

Slow Wave Activity (SWA) during recovery sleep was derived for each individual, due to its homeostatic role in regulating plasticity after sleep loss (Esser et al., 2007; Abel et al., 2013). Spectral analysis was performed on each 4-second epoch to calculate SWA at each electrode location. Power spectral density was calculated by use of a Fast Fourier Transform (FFT) on each hamming-windowed 4-second artifact-rejected epoch. FFT results were sorted according to sleep stage and averaged for each respective stage. SWA was calculated by integration across the EEG Delta frequency band, excluding frequency bins overlapping with slow artifact in the EEG. This yielded a final frequency window of 1–4.5 Hz, consistent with prior SWA investigations (Hz).

## Statistical approach

All statistical analyses were performed using STATA 11 (StataCorp LP, College Station, TX) in conjunction with the statistical toolbox in MATLAB R2012A (The Mathworks, Natick, MA) with the experimental hypothesis tested using the following three-step statistical analysis approach.

First, a one-way repeated-measures analysis of variance was performed on the separation bias measure of hippocampal-dependent learning, examining a main-effect of condition across the sleep rested/deprivation/recovery manipulations. Next, planned-comparisons were performed to examine the specific nature of any identified main effect by contrasting each pair of conditions (sleep deprivation, sleep rested and sleep recovered).

Second, to examine inter-individual levels of variability in vulnerability/resilience to sleep loss and sleep recovery participant-wise difference measures were calculated. Specifically the degree of deprivation-induced changes in learning was derived by subtracting performance under rested conditions from that under deprived conditions. This calculation resulted in a greater negative number indexing greater impairment. Similar metrics of restoration-success were derived by subtracting leanring performance under sleep deprivation conditions from that following the recovery nap. This calculation yielded higher positive numbers reflective of greater mnemonic restoration. These individual-difference metrics were first correlated with metrics of hippocampus subfield volume (*a priori* focus on the CA3/DG subfield region), and second with recovery NREM slow wave activity.

Third, to link the roles of brain structure and NREM sleep physiology in determining the functional consequences of sleep loss and recovery upon learning, a statistical path analyses was performed. To this end, an average SWA metric was calculated across those electrodes mutually predictive of deprivation-induced impairments and recovery-mediated restoration (T3, F7, and Cz). A series of directional multiple regression models were created examining the potential interactions of brain structure and NREM sleep physiology in this context. Specifically this model was specified using three regression equations:

| | Dependent Variable | = | Independent Variable 1 | + | Independent Variable 2 |
|---|---|---|---|---|---|
| **1** | Deprivation Impairment | = | CA3/DG Structure | | |
| **2** | Slow Wave Activity | = | Deprivation Impairment | + | CA3/DG Structure |
| **3** | Sleep Restoration | = | Slow Wave Activity | + | CA3/DG Structure |

These models offer the potential to elucidate between two distinct possibilities: (1) that SWA predicts restoration of learning without an influence of CA3/DG volume or (2) that SWA and CA3/DG volume are combinatory and interacting determinants of memory restoration.

## 2.3 Results

### Behavioral indices of impairment and recovery

A repeated-measures ANOVA demonstrated an expected main-effect of condition upon learning ($F(2,28) = 21.47$, $p < 0.001$; **Fig. 2.2**). Planned-comparisons confirmed a impairment following sleep deprivation, relative to the sleep rested condition ($t(14) = 4.90$, $p = 0.0002$), and a significant subsequent restoration following recovery sleep, relative to the sleep deprivation condition ($t(14) = 5.38$, $p = 0.0001$). Suggesting a return towards rested levels of performance, no significant difference was found between the rested and recovery conditions ($t(14) = -1.09$, $p = 0.29$).

### Predicting deprivation impairment

Although these results confirmed the expected memory impact of sleep deprivation and recovery sleep, marked variability was expressed across both manipulations. Targeting this variance, the severity of express learning impairment following sleep deprivation across participants was significantly and positively predicted by individual differences in the volume of the CA3/DG subfield ($r = -0.74$, $p = 0.002$, **Fig. 2.3A**). This effect was specific to CA3/DG, with the remaining hippocampal subfields (CA1: $r = -0.42$, $p = 0.11$, Subiculum: ($r = -0.51$, $p = 0.051$) not demonstrating the same strength of relationship.

### Predicting recovery restoration

Next, this study turned to whether CA3/DG subfield volume additionally predicted the beneficial impact of recovery sleep on learning restoration. While a positive relationship was identified, it was substantially weaker than with the impairment caused by prior sleep deprivation, reaching only trend-levels of significance ($r$ = 0.46, $p$ = 0.082, **Fig. 2.3A**). Turning instead to the hypothesized role of NREM physiology, recovery slow wave activity during the nap (SWA; a homeostatic marker of synaptic plasticity following sleep loss (Modirrousta et al., 2007)) over left frontal and temporal lobe EEG derivations positively and significantly predicted the degree of restored learning ability, while also indexing the magnitude of deprivation-impairment (F7: $r$ = 0.60 $p$ = 0.023; T3: $r$ = 0.57 $p$ = 0.034; Cz: $r$ = 0.69 $p$ = 0.007; Mean (as in **Fig 2.3B**): $r$ = 0.66 $p$ = 0.009). Thus, while hippocampal structure and SWA each positively predicted the success of memory restoration following recovery sleep, it was sleep physiology, and SWA specifically, that demonstrated the strongest association.

### Linking CA3/DG morphology and NREM slow wave activity

Although hippocampal structure and sleep physiology independently predicted the degree to which hippocampus-dependent learning was (1) susceptible to sleep loss, and (2) sensitive to recovery sleep, respectively, the weak (though positive) association between CA3/DG volume and memory restoration suggests that a more powerful explanation of recovery emerges not from SWA alone, but from the combined influence of CA3/DG volume and SWA. To test these interactions, a series of directional models formally examined two distinct possibilities: (1) that SWA solely predicts restoration of learning following sleep or (2) that memory restoration is predicted by a structural-physiological interaction of SWA and hippocampal CA3/DG volume.

These path analyses confirmed two findings (**Fig. 2.4**): (1) that the magnitude of learning restoration following sleep was directly predicted by SWA (β=0.55, $p$=0.029), yet (2), CA3/DG volume, while not a direct predictor of recovery (β=0.31, $p$=0.19), significantly accounted for such facilitation indirectly by determining the degree of mnemonic impairment under sleep deprivation (β=0.75, p=0.002), which, in turn, predicted the expression of SWA during recovery sleep (β=-0.78, $p$=0.05). Therefore, it was not the case that the restoration of learning following recovery sleep was accounted for solely by SWA. Rather, hippocampal brain volume represents an indirect determinant of this cognitive recuperation, by accounting for the degree of NREM SWA expressed during recovery sleep, and with it, the recovery of hippocampal learning.

## 2.4 Conclusions

Taken together, these findings demonstrate that the subfield structure of the human hippocampus significantly predicts (1) inter-individual vulnerability differences in the severity of learning impairment associated with sleep deprivation, and (2) the subsequent quality of NREM recovery sleep, following sleep deprivation, thereby determining the success of associated learning restoration. One potential mechanistic framework accounting for both these findings, and their

interaction, is the influence of the sleep-sensitive neurotransmitter adenosine on CA3/DG memory functioning, the details of which are outlined in the following sections.

## An adenosinergic framework of sleep deprivation in CA3/DG

Five lines of independent evidence support a potential link between the current bi-directional findings and adenosine. First, adenosine accrues in a manner proportional to extended time awake (Schmitt, Sims, Dale, & Haydon, 2012), representing an index of the severity of sleep loss (Schmitt et al., 2012), and subsequently decreasing across ensuing sleep (Porkka-Heiskanen, Strecker, Thakkar, et al., 1997; Porkka-Heiskanen, Strecker, & McCarley, 2000);. Second, the accumulation of adenosine within the hippocampal CA3 subfield region emerges though deposition by local neurons and astrocytes (Kawamura, Gachet, Inoue, & Kato, 2004; Florian, Vecsey, Halassa, Haydon, & Abel, 2011), both of which contribute to MRI-derived measured grey matter. Third, increased levels of adenosine functionally inhibit the induction of hippocampal long-term potentiation necessary for plasticity (Halassa et al., 2009; Havekes, Vecsey, & Abel, 2012), further associated with rodent learning deficits under conditions of sleep loss. Fourth, the impact of sleep deprivation upon hippocampal long-term potentiation (Vecsey et al., 2009) is blocked by adenosine-receptor antagonist caffeine (Alhaider, Aleisa, Tran, & Alkadhi, 2010), which in humans has recently been demonstrated to facilitate accurate hippocampal learning ability (Borota et al., 2014). Fifth, the degree of adenosine accumulation with continued wakefulness triggers a proportional increase in NREM SWA during subsequent recovery sleep (Benington, Kodali, & Heller, 1995), the magnitude of which determines the restoration of synaptic plasticity through its clearance of extra-cellular adenosine .

This collection of convergent evidence therefore provides a framework in which greater volume of the CA3/DG region—representing aggregated neuronal and astrocytic mass—will proportionally determine the extent of local adenosine accumulation across participants caused by sleep deprivation, which, in turn should determine the severity of associated learning impairment supported by this subfield region (here, pattern separation). Moreover, this same framework accounts for the recovery interactions with NREM sleep. Specifically, the extent of local adenosine accumulation across individuals, governed by the tissue volume of the CA3/DG volume, should index the consequential degree of homeostatic NREM SWA expressed during post-deprivation recovery sleep. Furthermore, the interaction of CA3/DG volume with NREM SWA should subsequently determine the success of extra-cellular adenosine clearance during recovery sleep, one outcome consequence of which would be the degree of hippocampal learning restoration supported by this region. This putative adenosinergic mechanism is consistent with recent evidence that adenosine receptor genetics, in part, moderate inter-individual differences in vunerabiltiy of performance to sleep deprivation (Rupp, Wesensten, Newman, & Balkin, 2013).

## Pattern separation in the broader context of sleep and memory

Pattern separation reflects the ability of the hippocampus to hold individual, yet related, memory representations separate (Yassa & Stark, 2011). Failure in such mechanisms may explain classic

findings that sleep stabilizes memory against retroactive interference occurring across wakefulness (Walker, 2009). For example, early research demonstrated that a sleep opportunity (approximately four hours after learning) preventing the normal decay-curve of forgetting that develops across time spent awake (Jenkins & Dallenbach, 1924). Moreover, recent work demonstrated that following sleep, compared to equal periods of wakefulness, specific memory associations (e.g. A-B) were less vulnerable to learned interference (e.g. A–C). One interpretation of this data is that following sleep, refreshed pattern separation allows the novel (A–C) memory to be stored in overlapping yet distinct hippocampal networks (Leutgeb & Leutgeb, 2007). In the case of prolonged wakefulness, a failure in pattern separation may result in a weaker original memory (A–B) trace, more susceptible to aberrant pattern completion (O'Reilly & Norman, 2002) by the novel conflicting memory (A–C). This failure of pattern separation under conditions of sleep loss offers one putative, and testable, framework explaining increases in retroactive interference in such conditions.

These data further offer potential insights in the context of situations where memory failure and sleep loss co-occur, particularly in context of aging. Recent findings have established that structural brain atrophy in older adults predicts the severity of NREM sleep impairment, resulting in diminished hippocampal memory function (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013; Mander, Rao, Lu, Saletin, Ancoli-Israel, et al., 2013). In addition, pattern separation within the hippocampus (Yassa, Mattfeld, Stark, & Stark, 2011)—and the CA3/DG region that regulates it (Yassa, Mattfeld, et al., 2011)—is particularly sensitive to effects of aging compared to other forms of memory processing. One intriguing hypothesis stemming from these two parallel lines of research in the context of the current findings is that age-related changes in CA3/DG subfield structure directly lead to changes in vulnerability of pattern separation-dependent learning in old age. Indeed, the positive relationship between CA3/DG volume and vulnerability in the current study—combined with evidence of normal age-related atrophy within the hippocampus—is consistent with evidence that older-age adults may be less vulnerable to sleep deprivation then young adults (Duffy, Willson, Wang, & Czeisler, 2009; Adam, Rétey, Khatami, & Landolt, 2006).

Moreover, these data suggest that deprivation-induced impairments on episodic declarative memory are rapidly reversible by recovery sleep. Such functional restoration of learning ability is consistent with those showing a short afternoon nap as sufficient to ameliorate the decay of learning ability across the day (Mander, Santhanam, et al., 2011; Antonenko et al., 2013). While the current study examines memory encoding processes, previous studies (e.g. (Yoo et al., 2007)) demonstrate that memory retrieval, conversely, remains impaired three days following sleep deprivation, despite intervening recovery sleep. Together these findings expand the current understanding of learning under conditions of sleep loss (Abel et al., 2013). That is, while the ability to learn new information may return after a short recovery sleep opportunity, information learned while sleep deprived remains inaccessible. The mechanisms that may or may not overlap in these two contexts remain unknown. Future studies using continuous recognition paradigms such as the current task will be strengthened by additionally including delayed tests of individual memories from each condition—in order to disentangle these unique time-courses of hippocampus functional recovery.

## Beyond learning and memory

Beyond learning, per se, these findings raise the question of whether individual differences in macroscopic brain morphology may further predict the impact of sleep loss on other functional domains. Across functional outcomes, repeated studies have demonstrated variable susceptibility to sleep loss, yet no clear biomarkers of these vulnerability phenotypes exist. Developing such a taxonomy could be informative for at least two reasons. First, they may shed insight into instances where sleep disturbance and cognitive impairment co-occur with changes in brain structure, as noted above (e.g. normative aging (Mander, Rao, Lu, Saletin, Lindquist, et al., 2013), degenerative dementia (Nho et al., 2012), obstructive sleep apnea (Joo, Tae, Lee, et al., 2010), and narcolepsy (Joo, Tae, Kim, & Hong, 2009)). Secondly, and of critical importance for the growing trend of curtailed sleep in society, these relationships may aid in predicting the severity of cognitive vulnerability to sleep loss in the occupations that regularly require individuals to restrict sleep (e.g., military, transportation, and medical professions) (Czeisler, 2011).

## 2.5 Tables

Table 2.1: Rested sleep statistics

| | Mean ± s.e. |
|---|---|
| Sleep Continuity | |
| Total Dark Time (min.) | $514.58 \pm 7.89$ |
| Total Sleep Time (min.) | $468.00 \pm 10.59$ |
| Sleep Efficiency (%) | $94.92 \pm 1.18$ |
| Latency to Sleep Onset (min.) | $18.56 \pm 4.99$ |
| Latency to REM Sleep (min.) | $89.57 \pm 9.07$ |
| Wake After Sleep Onset (min.) | $22.93 \pm 6.38$ |
| Sleep Architecture | |
| Stage 1 (% TST) | $4.72 \pm 0.60$ |
| Stage 2 (% TST) | $53.56 \pm 1.34$ |
| Stage 3 (% TST) | $12.57 \pm 0.06$ |
| Stage 4 (% TST) | $7.35 \pm 1.34$ |
| Slow Wave Sleep (% TST) | $19.92 \pm 1.81$ |
| REM Sleep (% TST) | $21.80 \pm 0.69$ |

Sleep Stages presented as % of Total Sleep Time. Slow Wave Sleep (Stages 3&4 NREM).

Table 2.2: Recovery sleep statistics

| | Mean ± s.e. |
|---|---|
| Sleep Continuity | |
| Total Dark Time (min.) | $87.33 \pm 2.06$ |
| Total Sleep Time (min.) | $82.02 \pm 1.95$ |
| Sleep Efficiency (%) | $97.57 \pm 0.72$ |
| Latency to Sleep Onset (min.) | $3.00 \pm 0.38$ |
| Wake After Sleep Onset (min.) | $1.69 \pm 0.58$ |
| Sleep Architecture | |
| Stage 1 (% TST) | $1.24 \pm 0.05$ |
| Stage 2 (% TST) | $25.75 \pm 2.46$ |
| Stage 3 (% TST) | $14.19 \pm 2.11$ |
| Stage 4 (% TST) | $52.50 \pm 3.21$ |
| Slow Wave Sleep (% TST) | $66.69 \pm 2.74$ |
| REM Sleep (% TST) | $6.19 \pm 1.93$ |

Sleep Stages presented as % of Total Sleep Time. Slow Wave Sleep (Stages 3&4 NREM).

## 2.6 Figures

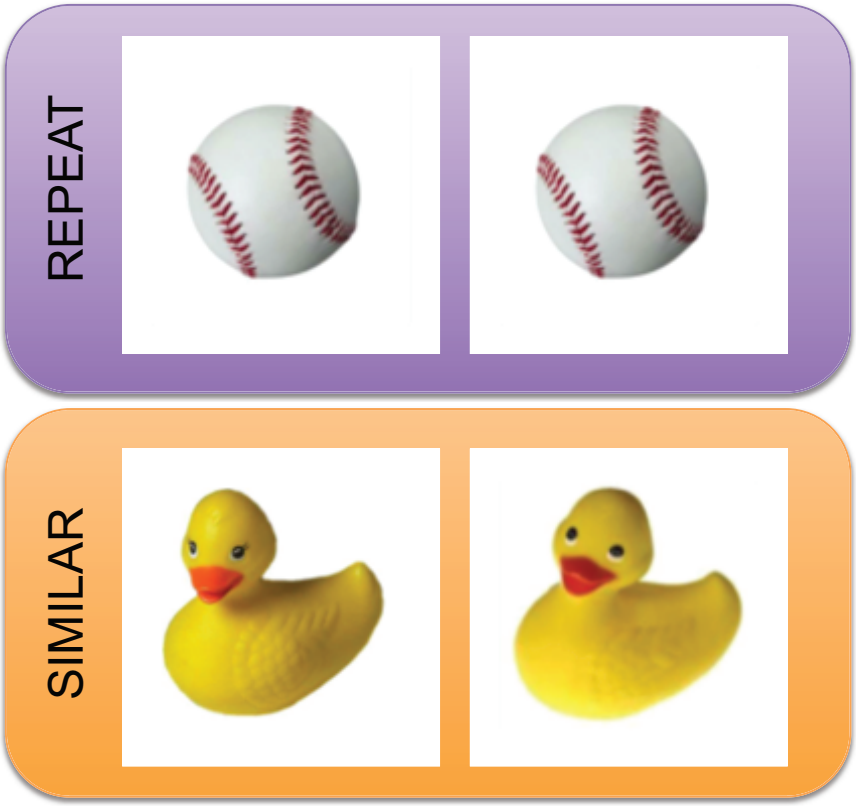


Figure 2.1: Example behavioral stimuli

(top) “Repeat pairs” involved the same image being displayed twice throughout the experimental protocol: once for initial encoding, once for later retrieval. (bottom) In contrast, the second image presentation for “similar pairs” was a modified, yet qualitatively similar, version of the initial image, such as the two toys presented here.

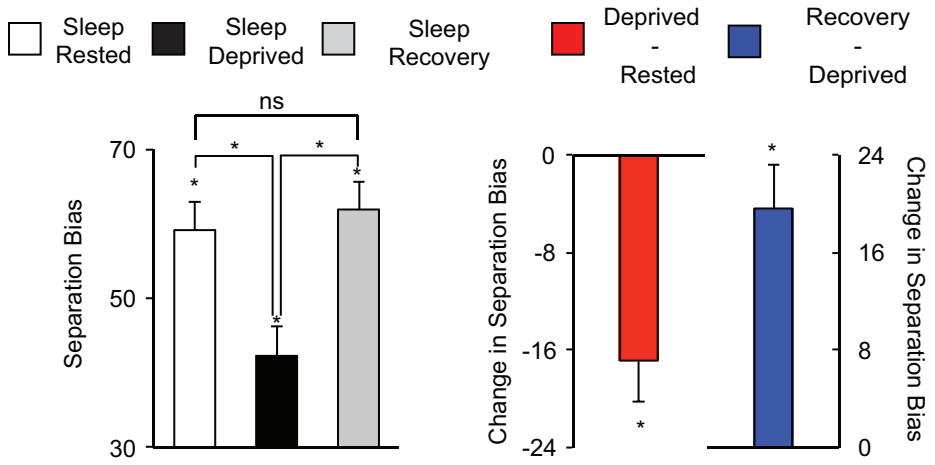


Figure 2.2: Behavioral learning performance following deprivation and recovery

(left) Learning ability (measured by pattern separation bias) at sleep rested (white bar), sleep deprived (black bar), and sleep recovery (grey bar) conditions, respectively. Comparison bars and asterisks reflect two-tailed t-tests between conditions. (right) Change in learning ability for sleep deprivation (deprivation - rested) and recovery (sleep recovery - sleep deprivation), respecitvely. Asterisks: ** = $p < 0.005$; * = $p < 0.05$; ns = non-significant.

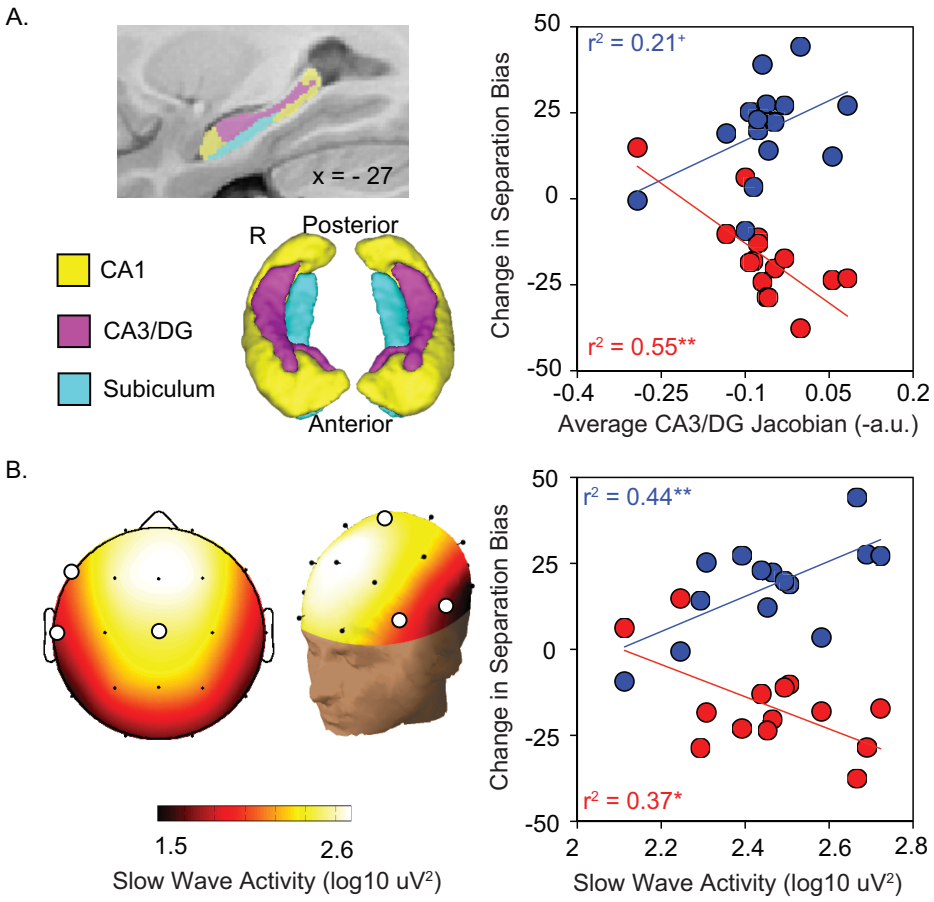


Figure 2.3: Relationship between hippocampus subfield structure and NREM slow wave activity with learning

(c) Associations with CA3/DG Structure. (left) Two-dimensional and three-dimensional representations of hippocampus CA1, CA3/DG, and Subiculum subfields. (right) Scatterplot relating change in pattern separation ability to CA3/DG volume. (b) Associations with recovery slow wave activity. (left) Two-dimensional and three-dimensional topographic plots of NREM slow wave activity during the recovery nap. White circles indicate the three electrodes (F7, T3, Cz) that were mutually predictive of both deprivation impairment, and recovery restoration, of learning (right) Scatterplot relating change in pattern separation ability to NREM slow wave activity (averaged accross F7, T3, Cz). Asterisks: ** = $p < 0.005$; * = $p < 0.05$

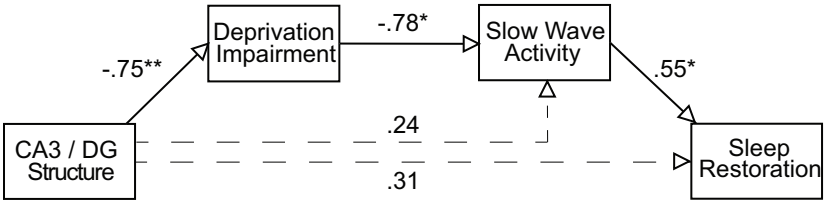


Figure 2.4: Path analysis exploring combined effect of hippocampus structure and NREM slow wave activity predicting learning recovery

LISREL-style model diagram, with associated standardized beta-weights from each component regression model (solid lines: significant paths; dashed lines: non-significant paths). Asterisks: ** = $p < 0.005$; * = $p < 0.05$.

# Chapter 3

# The Role of Sleep Spindles in Selective Remembering and Forgetting of Episodic Memory

Substantive evidence supports a role for sleep after learning in the offline consolidation of memory. However, circumstances exist where forgetting can be as critical as remembering, both in daily life and clinically. Using a directed forgetting paradigm, this study investigates the impact of explicit cue instruction during learning, prior to sleep, on subsequent remembering and forgetting of memory, after sleep. Sleep, relative to time awake, selectively ignored the facilitation of items previously cued to be forgotten, yet preferentially enhanced recall for items cued to be remembered; indicative of specificity based on prior waking instruction. Moreover, the success of this differential remember/forget effect was strongly correlated with fast sleep spindles—previously shown in **Study 1** to depend on hippocampal structure—over the left superior parietal cortex. Further, EEG source analysis of these spindles revealed a repeating loop of current density between selective memory-related regions of the superior parietal, medial temporal and right prefrontal cortices. These findings move beyond the classical notion of sleep universally strengthening information. Instead, they suggest a model in which sleep may be more ecologically attuned to instructions present during learning while awake, supporting both remembering and targeted forgetting of human memories.

## 3.1 Introduction

A substantive literature now implicates non-rapid eye movement (NREM) sleep, and its associated oscillations, in the consolidation and hence later recall of declarative memory (Mölle, Marshall, Gais, & Born, 2002; Schabus, Gruber, et al., 2004; Clemens, Fabo, & Halasz, 2005; Schmidt et al., 2006; Gais, Albouy, et al., 2007; Abel et al., 2013). However, the capacity to forget can, in certain contexts, be as important as the need for remembering, both in day-to-day life (e.g. forgetting last week's parking spot in preference for today's), and clinically (e.g. post-traumatic stress disorder and addiction). Item forgetting has been shown to decrease neural resources required for targeted remembering (Kuhl, Dudukovic, Kahn, & Wagner, 2007), and is considered to reflect a potential weakening or suppression of memory representations (Levy & Anderson, 2002). As a consequence, forgetting has been proposed to afford improved efficiency of subsequent recall under specific conditions (Block, 1971; Anderson, Ochsner, et al., 2004; Levy & Anderson, 2008).

Contrary to the role of sleep in subsequent remembering, earlier frameworks included speculation of a role for sleep in promoting forgetting (Ekstrand, 1967). Since the concept of memory weakening (Crick & Mitchison, 1983), the notion of sleep differentially modulating remembering and forgetting has remained relevant, considering the adaptive potential benefit of forgetting (Anderson, Ochsner, et al., 2004; Kuhl et al., 2007). Investigations examining emotional memory consolidation suggest that sleep may selectively treat some aspects of episodic experiences with preference over others. For example, a collection of reports have demonstrated that offline periods of sleep not only result in superior retention of emotional memories compared to neutral memories (Wagner, Gais, & Born, 2001; Hu et al., 2006; Nishida, Pearsall, et al., 2009), but benefit specific emotional aspects of these episodic experiences (Payne, Stickgold, Swanberg, & Kensinger, 2008; Payne & Kensinger, 2011), indicative of discriminatory processing. Despite these long-standing theoretical conceptions (Crick & Mitchison, 1983), a role for sleep in managing the offline balance between directed memory retention and forgetting remains untested. Moreover, the determinant mechanisms accounting for inter-individual differences in the success of such selective memory consolidation is unknown.

Targeting these questions, the current experiment utilized a validated directed forgetting task (Bjork, 1998; MacLeod, 1999; Lee, Lee, & Tsai, 2007; Wylie, Foxe, & Taylor, 2008; Hsieh, Hung, Tzeng, Lee, & Cheng, 2009; Nowicka, Marchewka, Jednoróg, Tacikowski, & Brechmann, 2011) to investigate the offline impact of sleep and wake on differential remembering and forgetting. Specifically, the study tested the hypothesis that, relative to equivalent time awake, sleep selectively facilitates recall of words previously cued for remembering, yet negates such facilitation of items instructed to be forgotten. Moreover, motivated by the homology in functional anatomy associated with fast frequency sleep spindles (Schabus, Dang-Vu, et al., 2007), and those networks known to support selective remembering and forgetting in specific fronto-parietal regions (Wylie et al., 2008; Nowicka, Marchewka, et al., 2011), this work sought to determine whether NREM fast sleep spindle oscillations promoted this differential directed forgetting memory effect.

## 3.2 Materials and Methods

### Participants Population

Forty-six healthy participants, age 18–30, were randomly assigned to either the Nap (n=23, 10 males, age 20.04 ± 2.08 [mean ± sd]) or the No-Nap (n=23, 10 males, age 20.89 ± 3.07 [mean ± sd]) group. Participants abstained from caffeine and alcohol for the 48 h before and during the entire course of the study, and kept a normal sleep-wake rhythm (7–9 h of sleep per night, with morning wake time between 06:30 and 08:30) for the two nights prior to study participation, as verified by sleep logs. Total sleep the night before testing did not differ between the Nap and No-Nap groups (7.89 hr ± 0.15, 7.65 hr ± 0.20 [mean ± se], respectively, $p$ = 0.34), and mean rise times also did not differ significantly between groups (08:33 ± 6min, 08:29 ± 5min [mean ± se], respectively, $p$ = 0.48). The study was approved by the local human studies committee, with all participants providing written informed consent. Participants were assigned to either a Nap group or a No-Nap group (**Fig. 3.1A**). Those in the Nap group were given 100-minute sleep opportunity from 14:30 to 16:10 whereas those assigned to the No-Nap group remained awake in the laboratory throughout the study-day, monitored by research personnel.

### Directed forgetting task

At 11:00, all participants, regardless of group assignment, were trained on a Directed Forgetting task (**Fig. 3.1a**). Conforming to previous paradigms (MacLeod, 1999; Lee, Lee, & Tsai, 2007; Wylie et al., 2008; Nowicka, Marchewka, et al., 2011), participants studied 100 words presented one at a time on a computer screen (gray background, black Courier New font, 50 point, center screen) for 2000 ms, followed by a 500 ms blank gray screen, after which a cue appeared instructing them to either remember (large green "R'') or forget (large red "F'') the previously presented word (both gray background, Courier New font, 150 point, center screen, 1000 ms; and see **Fig. 3.1B** for trial structure). Based on literature suggesting that post-cue intervals may impact rehearsal strategies, a short, restricted post-cue duration (time between offset of cue and onset of next trial) of 500 ms was used so as to circumvent rehearsal influences (MacLeod, 1999; Lee, Lee, & Tsai, 2007).

All words were chosen from the Pavio Word Generator (http://www.math.yorku.ca/SCS/Online/paivio/), creating 3 sets of 50 fifty words according to psycholinguistic descriptive statistics as in the directed forgetting paradigm of Wylie et al. (Wylie et al., 2008): Kucera-Francis word frequency (35.57±12.44, [mean ± sd], range: 20-50); concreteness rating (5.41±1.64, [mean ± sd], range: 2.0-7.0), meaningfulness (6.18 ± 0.90, [mean ± sd], range: 3.72-8.16), number of syllables (2.04 ± 0.93, [mean ± sd], range: 1.0-5.0), and number of letters (6.43 ± 2.08, [mean ± sd], range: 3.0-12.0).

To ensure equivalent and robust encoding of both word-types in both experimental groups (Nap and No-Nap), an immediate recognition test was performed following training at 11:15 (**Fig. 3.1A**) for half of the stimuli (25 words cued to be forgotten, 25 words cued to be remembered). Recognition testing, rather than free recall, was used for this immediate test in order to control

item exposure across all participants, prior to the wake or sleep experimental manipulation. This immediate recognition test contained 100 trials, 50 of which tested words seen during encoding (25 of each cue type), with an additional 50 novel words used as novel foils. Foils had the same psycholinguistic properties as the original words (see below). During each recognition trial, a word was presented on the screen for 1000 ms (gray background, black Courier New font, 50 point, center screen). After this presentation, the screen was cleared and participants were instructed to make a corresponding "old/new'' keypad judgment. The next trial did not begin until a response was given. As with encoding, all words were presented in a pseudo-randomized order, preventing more than four words of any one class from appearing successively. Recognition memory accuracy was calculated as the subtracted difference between the proportion of correctly identified "old'' words (hit rate), and the proportion of incorrectly identified "new'' words (false alarm rate) (Snodgrass & Corwin, 1988; Hornberger, Rugg, & Henson, 2006; Uncapher & Wagner, 2009; Vilberg & Rugg, 2008).

Following the offline sleep/wake manipulation (details below), both groups performed a five minute computerized delayed free recall test at 17:15 (**Fig. 1A**). Participants were instructed to freely recall as many words as they could from the initial learning (encoding) session, regardless of the cue previously associated with that word. Participants typed their entries one at a time on-screen and, after pressing the ENTER key, the answer was cleared and the next recalled word could be entered.

Free recall responses were classified as "R-words'' (recalled words previously cued to be remembered), "F-words'' (recalled words previously cued to be forgotten), "Foils'' (recalled words previously presented as foils during the immediate recognition test), and "Intrusion'' (recalled words never previously presented). Responses were also standardized as percentages of total recall (R-words + F-words + Error). This complementary way of evaluating recall success by standardizing to total recall amount is especially important considering that tests of free recall commonly lead to low word counts, including those of Directed Forgetting experiments (MacLeod, 1975; Bjork, 1998; MacLeod, 1999; Lee, Lee, & Tsai, 2007). An R-F difference measure, capturing the efficiency of the directed forgetting effect, was calculated by subtracting the proportion of F-words words recalled from the proportion of R-words words recalled. This R-F difference measure afforded a standardized score across participants, normalized to the number of recall attempts, similar to the principle of signal-detection theory in traditional memory paradigms (Snodgrass & Corwin, 1988).

## Sleep recordings

Those participants in the Nap group were given a 100-minute-sleep opportunity in the sleep laboratory from 14:30 to 16:10 (**Fig. 3A**) while those in the No-Nap group remained awake in the laboratory monitored by research personnel. Sleep recording methods were identical to those described in the prior studies. In short, polysomnography (PSG) sleep monitoring was recorded using a Grass Technologies Comet XL system (Astro-Med, inc., West Warwick, RI). Electroencephalography (EEG) was recorded at 19 standard locations conforming to the International 10-20 System (Jasper 1958). Electroculography (EOG) was recorded at the right and left outer canthi

while electromyography (EMG) was recorded via three electrodes (one mental, two sub-mental). Reference electrodes were placed at both the left and right mastoid (A1, A2). Data were digitized at 400Hz and stored unfiltered (recovered frequency range of 0.1–100 Hz), except for a 60-Hz notch filter.

Sleep Staging: Sleep-staging was performed, using C3, C4, O1, O2, right and left EOG, EMG, ECG channels. EEG and EOG were referenced to the contralateral mastoid, and filtered to 0.3-35 Hz. EMG and ECG each used a bipolar montage, and filtered to 10-70Hz and 0.1-12Hz, respectively. Sleep was visually scored in 30-second epochs using the C3-A2 derivation (Rechtschaffen & Kales, 1968).

## Sleep spindle analysis

Sleep spindles represent short synchronous bursts of activity related to hippocampal-dependent memory processing (Schabus, Gruber, et al., 2004; Clemens, Fabo, & Halasz, 2005; Diekelmann & Born, 2010; Abel et al., 2013). Furthermore, fast sleep spindles, rather than slow, are selectively associated with activity in the hippocampus, lateral and medial PFC, as well as posterior parietal regions (Schabus, Dang-Vu, et al., 2007). Moreover, it is variability in these fast-frequency sleep spindles that were identified in **Study 1** as being determined in part by underlying regional morphology of the human hippocampus. As such, and taken together with their proposed role in supporting memory consolidation, this study focused *a priori* on fast sleep spindles as a candidate for predicting the individual-levels of selective memory consolidation in the directed forgetting paradigm.

As in **Study 1**, sleep spindles were detected through an established algorithm (Ferrarelli et al., 2007; Nishida & Walker, 2007). In short (but see Ferrarelli et al. (2007) for details), the amplitude of the rectified signal from NREM sleep was used as a unique time series, identifying amplitude fluctuations exceeding threshold values, with the lower and upper values set at two and eight times the average amplitude. The peak amplitude for each spindle was defined as the local maximum above the threshold, with the beginning and end of the spindle defined as points immediately preceding or following this peak, when the amplitude of the time series dropped below the cut-off threshold. All EEG analyses were performed in MATLAB 7.5 (The Mathworks, Natick, MA), including the add-in toolbox EEGLAB (http://sccn.ucsd.edu/eeglab/).

Prior to analysis, each EEG channel was re-referenced to the average of the left and right mastoid, allowing for commonality of reference. NREM epochs were extracted based on visual scoring. All NREM epochs for each participant were concatenated into a single NREM time-series. Artifacts in the time series were removed by visual rejection. Following artifact-rejection, EEG was band-pass-filtered using a finite impulse response function, set between 12-15 Hz (frequency range defined by that used previously with the current algorithm (Ferrarelli et al., 2007), and commonly used for spindle detection (Eschenko, Mölle, Born, & Sara, 2006). The algorithm-determined spindles were restricted only to those events falling within this frequency range. The spindles were then classified as either fast (13.5–15 Hz) or slow (12–13.5 Hz). These frequency splits were derived from a median split of the frequency range of 12–15 Hz (Ferrarelli et al., 2007), similar to previous learning and memory studies (Knoblauch, Martens, Wirz-Justice, & Cajochen,

2003). Spindle density was calculated for each channel by dividing the number of spindles (fast or slow) by the total amount of NREM time (adjusted for artifact-rejected signal), representing the number of spindles occurring per minute in a given channel.

## sLORETA source analysis

To examine whether the regional brain generators of spindles may inform the anatomical basis of sleep-dependent memory consolidation an EEG source analysis of detected fast sleep spindles was performed. Scalp EEG represents the synchronous activity of many different neuronal sources. While multiple techniques exist to interrogate these neural sources of scalp EEG (Pascual-Marqui et al., 1999), one such solution, standardized low resolution tomography (Pascual-Marqui, 2002), allows for computations within a model based on the MNI152 template (Mazziotta et al., 2001). Such standard-space results allow for a facilitated comparison between sLORETA results and other neuroimaging modalities (as in **Study 1**). While the anatomical precision of sLORETA, and of all source analysis varies depending on EEG the number of electrodes in the EEG montage (Laarne et al., 2000), numerous studies have validated the sLORETA approach using montage arrays of similar resolution to that reported here (Pascual-Marqui et al., 1999; Isotani et al., 2001; Veiga et al., 2003; Bela et al., 2007; Clemens, Bank, et al., 2008; Tislerova et al., 2008; Clemens, Piros, et al., 2009; Ponomarev et al., 2010), or lower (Ventouras et al., 2007). Prior to source current-density calculation, all electrode channels were registered and transformed into 3D MNI space, yielding a spatial transformation matrix used to invert the EEG signal according to the sLORETA solution.

Continuous unfiltered NREM EEG was first marked for the onset of each fast spindle in a specified channel (Pz; identified in **Results**). A four-second epoch was then created around the spindle event: 1000 ms prior to spindle onset and the 3000 ms post-onset. Baseline correction was performed on each epoch (implemented with the EEGLAB function pop_rmbase), utilizing the 1000 ms prior to spindle onset, thereby correcting the remaining 3000 ms for baseline activity non-specific to the sleep spindle event. The 1000 ms baseline period was not included in further analyses. EEG epochs were averaged first within-participants and finally across the complete dataset, yielding a single 4000 ms grand-averaged "spindle''. Finally, to remove activity not related to sleep spindles, this grand-averaged EEG was filtered to the spindle frequency range (12–15 Hz). Separate sLORETA current-density was calculated for each time point in the 3000 ms time-series independently (at 400 Hz this represents 1200 unique time-points). Current-density maps were then rendered on un-inflated cortical surfaces (Holmes et al., 1998).

## Statistical analysis

Statistical analyses for this study were conducted in JMP 8.0 (SAS, Cary, NC). All p-values reported are two-tailed. Immediate recognition performance was submitted to paired and independent Student t-tests as appropriate for within- and between-subject comparisons, respectively. Delayed Free Recall data were analyzed first using a 2x3 mixed-level analysis of variance (ANOVA) with within-subject factor word-type (three levels: R-words, F-words, Error), and

between-subject factor group (two levels: No-Nap, Nap). The efficiency of directed forgetting, indexed by the R-F difference measure, was compared between groups using an independent Student t-test. The relationship between fast sleep spindles and directed forgetting memory performance was investigated via Pearson's bivariate correlation. Significance values were corrected for multiple comparisons at a family-wise error rate of $p < 0.05$.

## 3.3 Results

### Nap sleep statistics

Standard polysomnographic sleep statistics are provided in **Table 3.1**. Sleep architecture is presented as a percentage of Total Sleep Time. All participants in the nap-group achieved sleep, with 22 of 23 participants (95.7%) achieving slow-wave sleep (SWS; NREM Stages 3 and 4), and 17 of 23 participants (73.9%) achieving REM sleep.

### Immediate recognition

The results of the immediate recognition test are reported in **Table 3.2**. At immediate testing, when compared between groups, memory accuracy ([hit rate - false alarm rate]) was identical for both R-words ($t(44) = 1.37$, $p = 0.18$), and F-words ($t(44) = 0.97$, $p = 0.34$). Within each group, performance was significantly greater for R-words than for F-words (Nap: $t(22) = 9.43$, $p < 0.0001$, No-Nap: $t(22) = 8.25$, $p < 0.0001$). Furthermore, the difference in memory accuracy between R-words and F-words (R–F) was not significantly different between the two groups ($t(44) = 0.48$, $p = 0.63$). These findings indicate that, prior to any sleep or wake offline manipulation (a) the level of encoding for each word class was identical between the groups, (b) the task successfully led to the presence of a significant directed forgetting effect in both groups, and (c) the magnitude of this directed forgetting manipulation was equivalent between groups.

### Delayed free recall

Free recall performance is reported in **Table 3.2** and **Fig. 3.2**. Performance was collapsed across words that were either included or not in the immediate recognition test, as the exposure of a subset of items at this immediate test did not unduly influence the response (**Table 3.2**).

Following the sleep or wake offline periods, both groups recalled significantly more R-words than F-words ($F(2,43) = 58.06$, $p < 0.0001$; **Fig. 3.2A**). Additionally, there was a significant main effect of group ($F(1,44) = 6.44$, $p = 0.015$), with the Nap group recalling more words in total than the No-Nap group. Critically, this benefit of sleep was not due to equal improvement of both word types. Specifically, there was a significant group by cue-type recall interaction ($F(2,43) = 6.17$, $p = 0.004$), such that those in the Nap group, relative to the No-Nap group, showed a preferential recall of R-words, yet this benefit occurred in the absence of any such enhanced recall of F-words. Thus, sleep did not ubiquitously facilitate all items. Instead, sleep provided a superior recall advantage

for words previously cued for remembering, but did so without concomitant enhancement of items previously cued for forgetting, indicative of specificity based on prior waking instruction. One alternative explanation is that sleep-enhanced memory of the cue-associations, rather than modulating the word-items themselves, allowing facilitation of knowledge in the nap-group of which items to recall. This appears unlikely, however, since the Nap group, relative to the No-Nap group, showed no converse decrease in recall for items cued to-be-forgotten.

The effectiveness of directed forgetting on free recall was further characterized as a proportional difference-score. Specifically, the number of F-words recalled was subtracted from the number of R-words recalled (expressed as proportion of total recall), yielding the R-F efficiency score. This difference measure further demonstrated significantly greater recall of R- relative to F-words in the Nap relative to No-Nap group ($t(44) = 2.18$, $p = 0.03$; **Fig. 3.2B**). Therefore, based on instruction given during initial learning, and compared to equivalent time awake, sleep was capable of more efficiently managing the balance between differential later recall of items cued for remembering relative to those cued for forgetting.

## Sleep physiology associations

Following analysis of directed forgetting behavioral performance after sleep, the study next sought to determine whether aspects of sleep physiology within the Nap group were associated with the observed selective enhancement to words cued to be remembered and not to words cued to be forgotten. Analyses focused a priori on fast sleep spindles, based on their associated functional anatomy (Schabus, Dang-Vu, et al., 2007; Nishida & Walker, 2007) converging with that anatomy supporting directed forgetting (Wylie et al., 2008; Nowicka, Marchewka, et al., 2011), as well as their structural determinants (**Study 1**) indicating a unique relationship with the hippocampus, compared to slow frequency spindles. As with recent work demonstrating local physiological, beyond global sleep stage associations with memory (Huber et al., 2004; Marshall, Helgadóttir, et al., 2006), strong and significant relationships between fast sleep spindles and the directed forgetting efficiency score (R-F) in multiple posterior electrode sites (**Fig. 3.3B**): F8 ($r = 0.46$, $p = 0.03$), C4 ($r = 0.42$, $p = 0.049$), T4 ($r = 0.44$, $p = 0.04$), P3 ($r = 0.66$, $p = 0.0006$), Pz ($r = 0.56$, $p = 0.006$), P4 ($r = 0.53$, $p = 0.0098$), and O1 ($r = 0.49$, $p = 0.012$), with significance at P3, situated over the left superior parietal lobe and commonly associated with episodic memory processing (Uncapher & Wagner, 2009), retained significance (**Fig. 3.3C**, $r = 0.66$, $p = 0.0006$). Correlation analyses with slow spindle-density and the R-F difference measure demonstrated a positive association at electrode site T6 ($r = 0.43$, $p = 0.041$), which did not survive correction for multiple comparisons.

In addition to the predictive spindle relationship with the R-F difference score, fast sleep spindles predicted recall of R-words and F-words independently, and in opposing directions. Specifically, fast spindles (a) significantly and positively correlated with the proportion of R-words recalled at a number of posterior parietal sites: P3 ($r = 0.59$, $p = 0.003$), Pz ($r = 0.48$, $p = 0.021$), P4 ($r = 0.47$, $p = 0.025$), and O1 ($r = 0.45$, $p = 0.030$), yet (b) negatively correlated with the proportion of F-words recalled at a number of frontal sites: C3 ($r = -0.43$, $p = 0.04$), Fp1 ($r = -0.49$, $p = 0.017$), Fp2 ($r = -0.48$, $p = 0.02$), F7 ($r = -0.57$, $p = 0.0044$), and F8 ($r = -0.50$, $p = 0.016$). However, none of these correlations survive correction for multiple comparisons, and no relationships were iden-

tified between slow spindles and R- or F-words (p's > 0.05). Therefore, while fast sleep spindles did differentially predict the recall of R- and F-words independently, these relationships were markedly less significant than that identified for the R-F efficiency score, with only the latter surviving correction for multiple comparisons. Such findings support a framework whereby sleep spindles modulate the proportional balance between remembering and forgetting (encapsulated by the R-F efficiency score), beyond modulating either of these word types independently.

### sLORETA source analysis

Considering the hypothesized role of parietal-frontal networks, combined with medial-temporal lobe structures, in episodic memory processing (Uncapher & Wagner, 2009; Shimamura, 2011), sLORETA source analysis was used to characterize the neural sources of the identified P3 fast sleep spindles. Since sleep spindles have no one peak, current source density was calculated across the spindle time-series (**Fig. 3.4**). This time-course analysis revealed a repeating loop of activity throughout a network in the superior parietal cortex, lateral prefrontal cortex as well as anterior and posterior cingulate cortex (**Fig. 3.4**). This recursive pattern of regional source activity is of note considering the congruent overlaps with networks previously implicated in supporting selective remembering and forgetting of memories (Wylie et al., 2008; Hauswald, Schulz, Iordanov, & Kissler, 2011; Nowicka, Marchewka, et al., 2011).

## 3.4 Conclusions

A corpus of evidence implicates NREM sleep physiology in the consolidation of episodic declarative memory, leading to superior memory retention relative to equivalent time periods awake (Abel et al., 2013). In previous study designs, participants are either explicitly informed of a later retrieval test at the time of initial encoding, thereby emphasizing a need for remembering (Gais, Mölle, et al., 2002; Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009), or are not made aware of the later post-sleep test (Gais, Lucas, & Born, 2006; Wagner, Hallschmid, Rasch, & Born, 2006; Ellenbogen, Hu, Payne, Titone, & Walker, 2007; Yoo et al., 2007; Schabus, Hoedlmoser, et al., 2008; Tucker & Fishbein, 2008). It has therefore remained unclear whether selective cue instruction for remembering or forgetting at the time of initial learning, prior to consolidation, has a significant impact on the degree of subsequent successful recall, following offline time delays. Furthermore, and related to theoretical proposals (Freud, 1913; Crick & Mitchison, 1983), an additionally untested hypothesis is whether the offline consolidation trajectory of instructed remembering and forgetting is modulated by the different brain-states of wake or sleep (or specific sleep-stage physiology). Considering the proposed adaptive function of forgetting, affording reduced competition amongst relevant representations (Block, 1971; MacLeod, 1999; Anderson & Green, 2001; Levy & Anderson, 2002; Anderson, 2003), a role for sleep in the balanced dynamics of remembering and forgetting increases in potential relevance.

Focusing on these questions, the current findings contribute to a progressively more nuanced understanding of sleep-dependent memory processing, complementing but also moving beyond the established notion of sleep universally strengthening information (Marshall & Born, 2007; Walker, 2009; Diekelmann & Born, 2010). Instead, these data suggest a more nuanced role for sleep in differentially gating the selective offline consolidation of memories, based on prior waking instructions, leading to the selective remembering and forgetting of discreet item information. Specifically, while both the Nap and No-Nap groups expressed equivalent proportions of cued remembering and forgetting at immediate testing, indicated robust encoding of both these item types, the subsequent offline periods of wake or sleep resulted in significantly different recall rates for each item class. Sleep, relative to wake, preferentially facilitated one class of cued items—those instructed to-be-remembered—without facilitating another class of cued items—those instructed to-be-forgotten. As a result, sleep served to more efficiently maximize the directed forgetting effect; a process conceptually similar to an improved signal (R-words) to noise (F-words) retention ratio. It is of note that these findings differ to previous reports demonstrating a uni-directional benefit of sleep in the prevention of forgetting over time, which did not involve or examine the impact of instructional manipulation of encoding prior to sleep (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Baran, Wilson, & Spencer, 2010; Racsmány, Conway, & Demeter, 2010), nor assessed intentional forgetting, rather than attempted memory suppression (Fischer, Diekelmann, & Born, 2010). In contrast, the current study demonstrates a differential sensitivity of the sleep-dependent consolidation process towards intentional and adaptive forgetting and remembering (Anderson, 2003), based on explicit prior waking instruction.

In addition to between-group differences in directed forgetting, and moving beyond sleep-stage associations (Fischer et al., 2010), strong predictive relationships were identified between the efficiency of the directed forgetting effect and fast sleep spindles in the Nap group, especially at electrode P3 located over left superior parietal cortex. Consistent with the hypothesis of sleep governing the bi-directional modulation of each item class, fast spindles separately and positively correlated with the proportion of words cued for remembering at posterior parietal regions, yet negatively correlated with words cued for forgetting at several frontal locations. Although it is important to note that these correlations for each word class alone did not survive correction for multiple comparisons, the inverse nature of these relationships suggests that the correlation identified with the R-F difference measure was not simply driven by an exclusive association with R-words (or F-words) alone.

These associations build on an increasing collection of reports implicating sleep spindles in memory processing, describing learning-dependent increases in spindles following initial memory encoding (Gais, Mölle, et al., 2002; Eschenko et al., 2006; Fogel, Smith, & Beninger, 2009; Morin et al., 2008; Fogel, Smith, & Beninger, 2009), as well as correlations (often topographic) with the success of post-sleep memory retention (Clemens, Fabo, & Halasz, 2005; Clemens, Fabó, & Halász, 2006; Fogel & Smith, 2006; Nishida & Walker, 2007; Tamaki, Matsuoka, Nittono, & Hori, 2008). Our findings further suggest that spindles can additionally support the differential later recall of items cued for remembering, yet do so without a concomitant facilitation of items cued for forgetting, indicative of selectivity, rather than indiscriminant facilitation.

Conceivably, such a process of specificity would require an offline mechanism capable of supporting item selection, based on prior cues and the subsequent preferential consolidation of these selected representations. Properties of sleep spindles appear well positioned to support such processing for a number of potential reasons. First, neuroimaging studies have identified inferior prefrontal, superior parietal and medial temporal lobe structures in promoting successful instructed remembering over forgetting (Anderson, Ochsner, et al., 2004; Kuhl et al., 2007; Wylie et al., 2008; Hauswald, Schulz, et al., 2011; Nowicka, Marchewka, et al., 2011), regions that overlap with those associated with fMRI correlates of fast sleep spindles (Schabus, Dang-Vu, et al., 2007; Wylie et al., 2008). Second, previous EEG studies further indicate strong spindle-dependent coherence between homologous frontal and parietal networks (Achermann & Borbély, 1998; Ventouras et al., 2007; Gumenyuk et al., 2009). Third, surface spindles are temporally linked with sharp-wave ripples occurring in the hippocampus and surrounding rhinal cortex (Marshall & Born, 2007; Abel et al., 2013), the activity of which is proposed to play a role in dynamics of hippocampal-neocortical memory processing (Mölle, Marshall, et al., 2002; Schabus, Gruber, et al., 2004; Clemens, Fabo, & Halasz, 2005; Schmidt et al., 2006; Gais, Albouy, et al., 2007; Diekelmann & Born, 2010; Abel et al., 2013). Forth, source analyses of fast spindles in the current study revealed a similar convergent network of recurrent activity in superior parietal, temporal and inferior frontal cortex. Based on this evidence, such spindle activity may provide a putative anatomical framework (see **Fig. 3.5** for an anatomical heuristic) for selective item offline memory processing. In such a model, parietal cortex would allow for the binding of top-down intentional information (e.g. selective cues) sourced from prefrontal cortex, with bottom-up item memory information from medial temporal areas, including hippocampus (Shimamura, 2011), resulting in selective and discriminatory item consolidation.

A consideration when using the item-method of directed forgetting is that of selective rehearsal for R-words versus F-words at the time of encoding, if a sufficient post-cue time lag is allowed prior to the next item presentation (MacLeod, 1999). Our current paradigm deliberately used a short post-cue interval (500ms) to minimizes these effects, as have others (e.g. Lee, Lee, and Tsai (2007)). It is also important to note that a collection of recent findings have provided evidence that, beyond selective rehearsal, active intentional processes underlie direct remembering and forgetting using the item method (Lee, Lee, & Tsai, 2007; Fawcett & Taylor, 2008; Hauswald & Kissler, 2008; Wylie et al., 2008; Hsieh et al., 2009; Nowicka, Jednoróg, Wypych, & Marchewka, 2009; Van Hooff, Whitaker, & Ford, 2009). For example, Wylie and colleagues (Wylie et al., 2008) have demonstrated that BOLD activity during encoding of intentionally forgotten (misses on F-word trials), compared to unintentionally forgotten (misses on R-word trials), exhibited increased activity in frontal inhibitory regions (superior, middle, and inferior frontal gyri). This evidence indicates that intentional forgetting is not identical to passive decay of words items, which would be predicted in an account of directed forgetting attributing the effect solely to selective rehearsal of remember words. Further, this report described differences in middle frontal gyrus, cingulate gyrus in the contrast between intentionally forgotten and intentionally remembered trials, taken to indicate top-down frontal inhibitory processes supporting directed forgetting. Using event-related potentials (ERPs), Van Hooff and colleagues (Van Hooff et al., 2009) have additionally identified late evoked potentials in the 500 – 700 ms post stimulus onset

that were less negative for correctly forgotten words, cued to be forgotten, compared to cued to be remembered words that were actually forgotten, or correct rejections of new words as seen by Nowicka and colleagues (Nowicka, Jednoróg, et al., 2009), suggesting that neural processing of intentional forgetting (failure to recall F-words) is distinct from that of unintentional forgetting (failure to recall remember words). Fawcett and colleagues (Fawcett & Taylor, 2008) have also demonstrated significantly increased latencies to reaction time probes placed after the cue for F-word trials, compared to R-word trials. A selective rehearsal account would expect opposite, as participants would be distracted during elaborate rehearsal. Instead the results suggest that there is an active inhibition processes taking place during explicit instructed forgetting trials. Together, these studies move beyond a selective rehearsal account of directed forgetting, where distinct neural processes distinguish incidental forgetting (forgetting of R-words) from intentional forgetting (forgetting of F-words). Within the context of these studies, combined with the short post-cue interval using in the current study, and that participants in both the nap and no-nap groups demonstrated robust immediate recognition and later recall for forget words (**Table 3.2**, our findings appear best considered in a framework of active remembering and forgetting, rather than different selective rehearsal at the time of encoding.

In summary, this study demonstrates that sleep, relative to time awake, can selectively enhance recall for words previously cued for remembering, without such facilitation of items instructed to be forgotten. Moreover, the efficiency of sleep in differentially responding to cued remembering and forgetting correlated with fast sleep spindles over left parietal cortex. Further, source analysis associated with these spindles identified a network-loop of current-density between parietal, medial temporal and prefrontal memory networks that may support selective offline memory processing. More generally, the concept of sleep differentially modulating memory based on prior cue instructions may have implications clinically, where the capacity for selective retention of certain information, while forgoing maintenance of unwanted experiences, represents a desirable target.

## 3.5 Tables

Table 3.1: Nap-group sleep statistics and correlations with directed-forgetting performance

| | mean $\pm$ s.e. | R-word $r(p)$ | F-word $r(p)$ | R-F $r(p)$ |
|---|---|---|---|---|
| Total Sleep Time (min) | $80.09 \pm 3.61$ | $-0.19\ (0.38)$ | $-0.08\ (0.70)$ | $-0.15\ (0.49)$ |
| Stage 1 % | $10.94 \pm 1.33$ | $-0.20\ (0.35)$ | $-0.39\ (0.063)$ | $0.31\ (0.15)$ |
| Stage 2 % | $37.12 \pm 2.75$ | $-0.01\ (0.97)$ | $-0.40\ (0.056)$ | $0.12\ (0.60)$ |
| SWS % | $23.84 \pm 2.93$ | $-0.23\ (0.29)$ | $0.52\ (0.012)$ | $-0.37\ (0.08)$ |
| REM % | $8.27 \pm 1.71$ | $-0.23\ (0.44)$ | $-0.11\ (0.92)$ | $-0.12\ (0.59)$ |

Sleep Stages presented as % of Total Sleep Time. SWS: Slow-wave sleep (Stages 3&4 NREM). P values in bold are significant at $p < 0.05$. P-values from correlation analyses of sleep statistics and free recall performance.

Table 3.2: Directed forgetting performance and between group statistical comparisons

| | No-Nap | Nap | $p$ |
|---|---|---|---|
| Immediate Recognition Test | | | |
| R-words | | | |
| HR | $0.84 \pm 0.03$ | $0.83 \pm 0.03$ | 0.959 |
| FA | $0.24 \pm 0.03$ | $0.17 \pm 0.02$ | 0.057 |
| Memory Accuracy | $0.60 \pm 0.04$ | $0.66 \pm 0.03$ | 0.178 |
| F-words | | | |
| HR | $0.56 \pm 0.03$ | $0.53 \pm 0.03$ | 0.304 |
| FA | $0.24 \pm 0.03$ | $0.17 \pm 0.02$ | 0.057 |
| Memory Accuracy | $0.32 \pm 0.04$ | $0.37 \pm 0.03$ | 0.337 |
| R-F (Memory Accuracy) | $0.28 \pm 0.03$ | $0.30 \pm 0.03$ | 0.630 |
| Free Recall Test | | | |
| R-words | $6.96 \pm 0.66$ | $13.34 \pm 2.03$ | 0.005 |
| "Re-exposed" | $4.74 \pm 0.49$ | $7.83 \pm 1.07$ | 0.012 |
| "Not Re-exposed" | $2.21 \pm 0.33$ | $5.52 \pm 1.03$ | 0.004 |
| F-words | $1.91 \pm 0.28$ | $1.87 \pm 0.42$ | 0.933 |
| "Re-exposed" | $1.48 \pm 0.31$ | $1.57 \pm 0.38$ | 0.860 |
| "Not Re-exposed" | $0.43 \pm 0.13$ | $0.30 \pm 0.12$ | 0.445 |
| Error | $4.52 \pm 0.72$ | $4.74 \pm 1.34$ | 0.876 |
| "Re-exposed" | $1.09 \pm 0.23$ | $0.74 \pm 0.21$ | 0.266 |
| "Not Re-exposed" | $3.43 \pm 0.70$ | $4.00 \pm 1.13$ | 0.672 |
| Total Recall (R + F + Error) | $13.39 \pm 0.97$ | $19.96 \pm 2.39$ | 0.015 |
| R% (% Total Recall) | $0.54 \pm 0.05$ | $0.67 \pm 0.05$ | 0.066 |
| F% (% Total Recall) | $0.013 \pm 0.02$ | $0.09 \pm 0.02$ | 0.091 |
| R-F% (% Total Recall) | $0.41 \pm 0.05$ | $0.57 \pm 0.05$ | 0.035 |

HR: Hit Rate, FA: False Alarm Rate. Memory Accuracy: HR-FA. "Re-exposed": Words tested at immediate recognition, "Not Re-Exposed", words not tested at immediate recognition. P-values from two-tailed independent-sample t-tests.

## 3.6 Figures

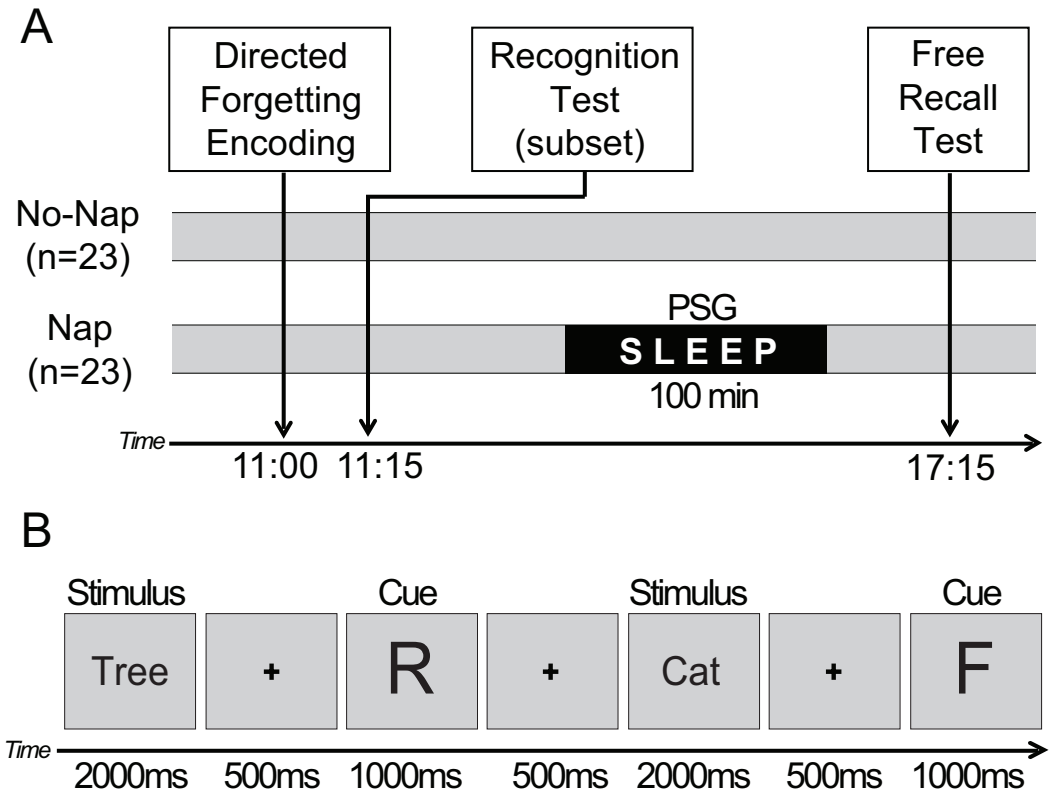


Figure 3.1: Study design

(a) Time-course of experiment for both the No-Nap and Nap groups respectively, describing training, immediate test, and delayed test sessions. The nap involved a 100-minute sleep opportunity from 14:30 to 16:10 recorded using 19-channel EEG polysomnography (PSG). (b) Schematic for the Directed Forgetting task, demonstrating two representative trials. Words were presented in the center of the screen for 2000 ms, followed by a fixation cross for 500 ms, and then a large letter cue indicating that participants should remember the prior word ("R"), or forget the prior word ("F"). While these R and F cues are shown in black font in the schematic, they were green and red, respectively, in the actual task.

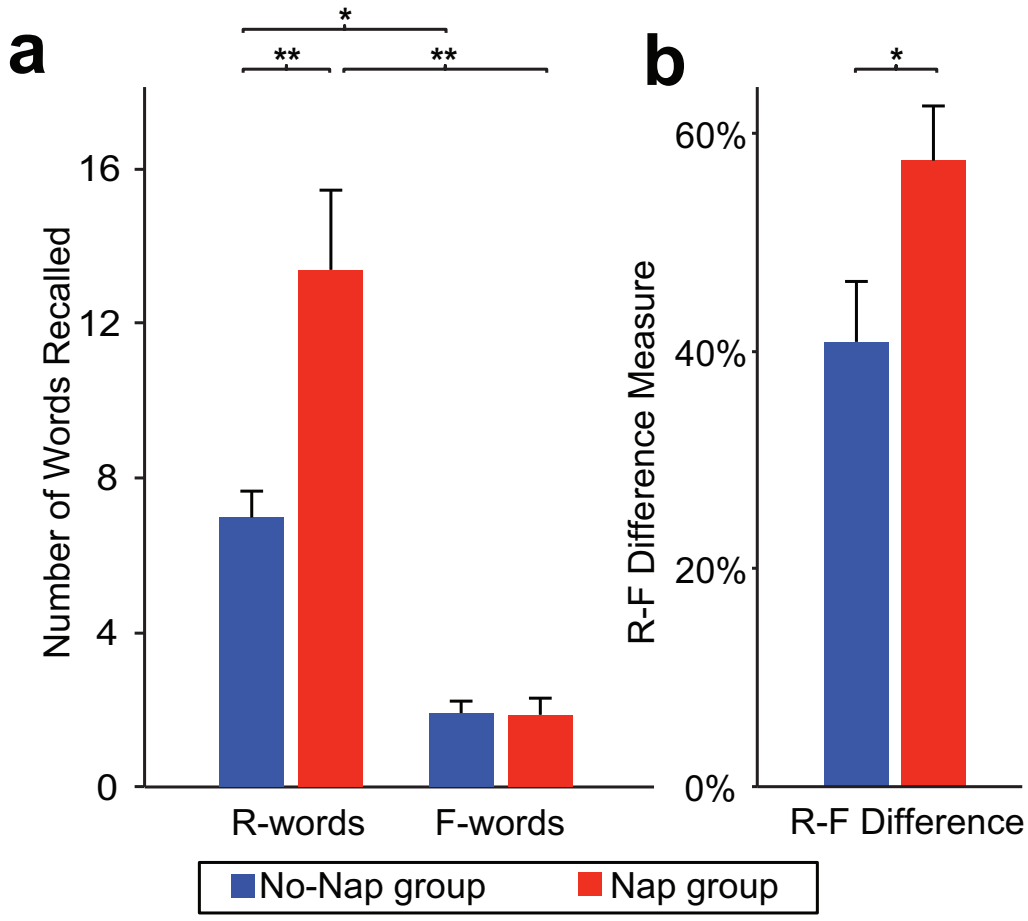


Figure 3.2: Behavioral results

(a) Number of words recalled based on prior cue instruction (Remember, R-words; Forget, F-words) in the Nap and No-Nap groups, and (b) the efficiency measure of directed forgetting, calculated as the subtraction of these scores (R-F; expressed as a proportion of total recall; supplemental information). Between group comparisons (line across bars) reflect significance at: $* : p < 0.05$ and $** : p < 0.01$. Error bars represent s.e.m.

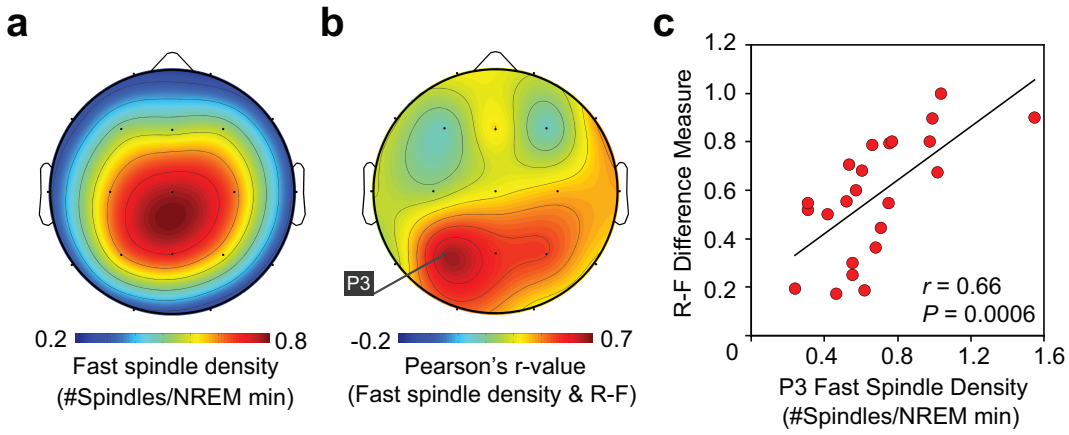


Figure 3.3: Relationship between memory performance and sleep spindles

(a) Topographic plot for fast sleep spindle density in the nap-group (color bar indicates density [number of spindles/minute of NREM]), (b) correlation topographical plot demonstrating strength of relationship between fast sleep spindle density and R-F score. Note spindle activity at the P3 (left parietal) electrode site showing the strongest relationship (color bar indicates Pearson $r$, with noted corresponding critical $p$-value increments), (c) scatter-plot and linear regression of the relationship between fast sleep spindle density at P3 and the R-F score across participants in the nap-group.

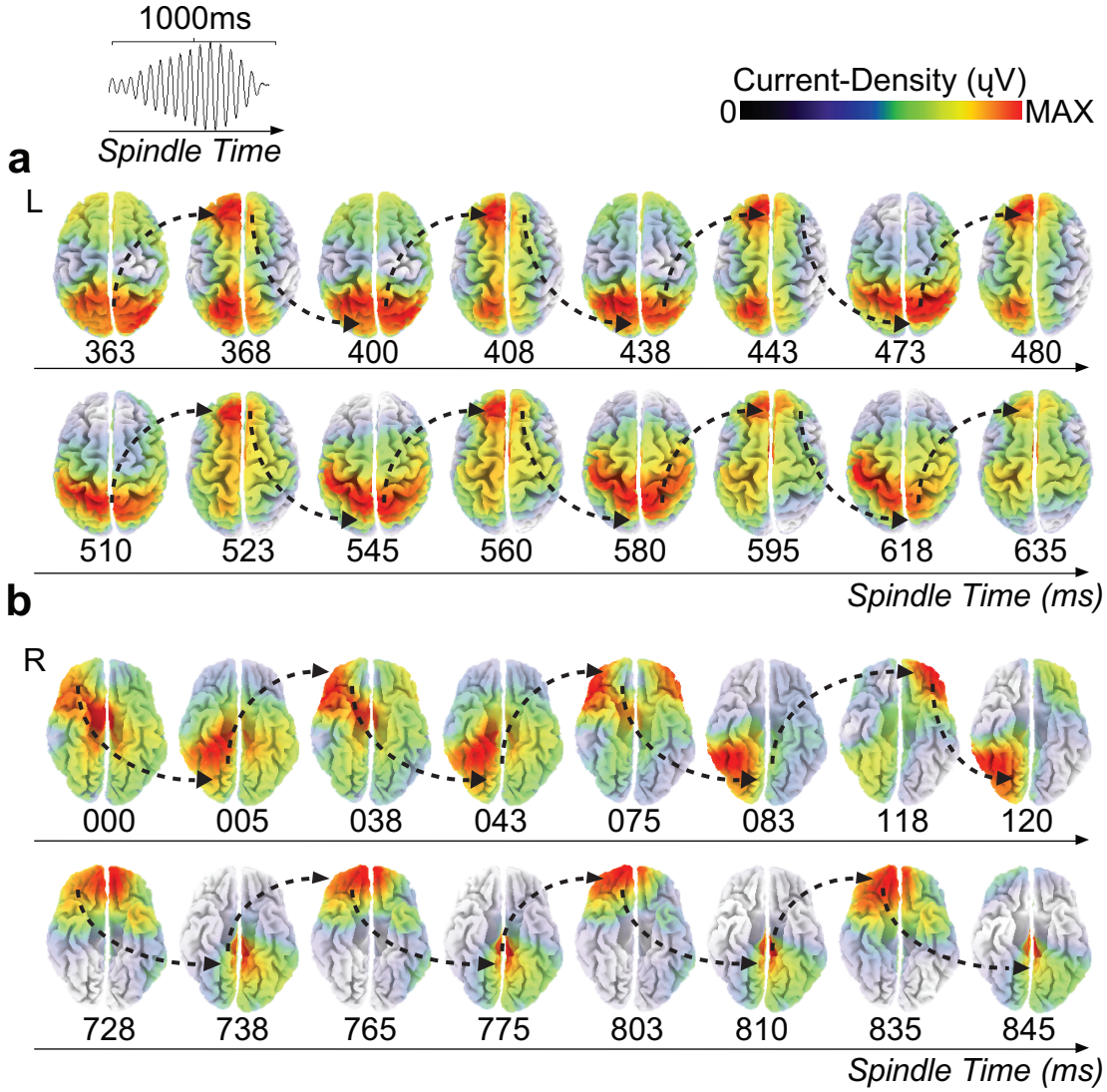


Figure 3.4: sLORETA Spindle Source Analysis

sLORETA source of fast sleep spindles identified by onset in P3 (P3 spindle shown in upper left), demonstrating a propagation loop of current-density between frontal, medial-temporal and parietal networks across the spindle time-series. Columns represent time points. Current-source density plotted on inflated (a) superior and (b) inferior cortical surfaces. Time in milliseconds is given below each column, relative to the onset of the sleep spindle. Color bar represents the sLORETA dynamic current density across the time series. Dash-arrows indicate the dominant movement of current-density in the reoccurring loop.

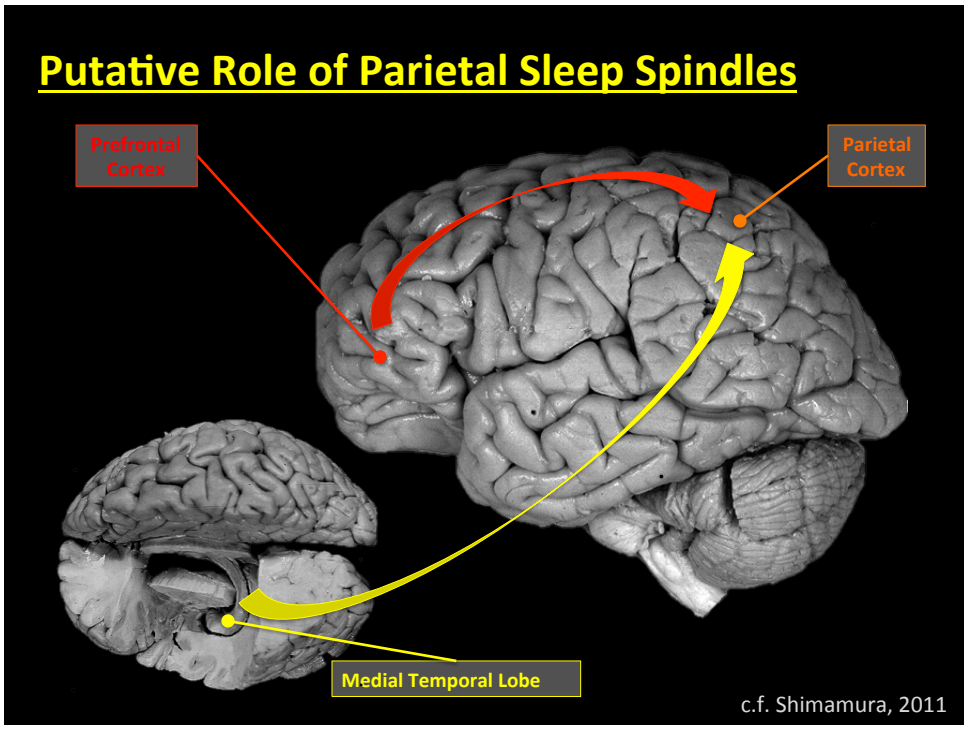


Figure 3.5: Parietal sleep spindles: top of anatomical memory network

sLORETA source analyses identify the medial temporal lobe (yellow), prefrontal cortex (red), and superior parietal cortex (orange) as an oscillatory loop of areas active during fast sleep spindle oscillations. These areas a reconsistent with a recently proposed model of memory by which the parietal cortex integrates top-down intentional signals from the prefrontal cortex with bottom-up memory representations in the medial temporal lobe (Shimamura, 2011). As such sleep spindle putatively reiterate this integration during sleep, leading to strengthening of selective consolidation cues (i.e. which memeories “to remember” and which “to forget”

# Conclusions

*I love sleep. My life has the tendency to fall apart when I'm awake.*

– Ernest Hemingway

By combining structural MRI, sleep EEG, and cognitive paradigms of learning and memory, this thesis offers three core findings: **Study 1** demonstrates that inter-individual variability in NREM physiology is accounted by grey matter morphology in functionally relevant brain regions. Specifically, grey matter volume in the homeostatic sleep-regulating center of the basal forebrain/hypothalamus, together with the medial prefrontal cortex, accounted for individual differences in NREM slow waves. In contrast, grey matter volume in interoceptive and exteroceptive cortices predicted slower NREM sleep spindles frequencies, while grey matter volume in bilateral hippocampus was associated with faster NREM sleep spindle frequencies. **Study 2** establishes that the structural integrity of the hippocampus—and particularly the CA3/DG subfield—accounts for inter-individual differences in the vulnerability impact of sleep deprivation on learning impairment, as well as subsequent mnemonic restoration by NREM SWA during recovery sleep. Finally, **Study 3** suggests a beneficial influence of NREM sleep spindles in differentially gating the selective offline consolidation of memories, based on prior waking instructions, leading to the selective remembering and forgetting of discreet item information. While each of these findings have been discussed individually in the respective discussion sections above, the following conclusion section will close by considering commonalities across studies, and their combined translational relevance.

## Brain structure and sleep-dependent cognition: Translational relevance

Results from all three studies offer the potential to bridge the independent findings of cognitive impairment and co-morbid sleep disruption in several neurological and psychiatric disorders. Arguably, the two most prescient examples of these interactions are post-traumatic stress disorder (PTSD), and attention-deficit-hyperactivity disorder (ADHD).

*PTSD:* A growing literature has examined disturbed sleep as a potential precipitating component of PTSD (Germain, 2013), yet the underlying mechanism linking these two features remains largely unknown. Evidence from **Studies 1** and **3** suggest that hippocampal brain structure, in combination with sleep spindles, may represent one such mediating pathway. Specifically, **Study 3** demonstrates fast sleep spindles can govern selective remembering and forgetting of

episodic experiences, the latter being of relevance as a therapeutic goal in the context of PTSD trauma memories. Moreover, the results of **Study 1**, linking fast sleep spindle generation to hippocampus structural integrity, offer additional relevance considering the known reductions in hippocampal volume in PTSD (Woon, Sood, & Hedges, 2010). Indeed, sleep quality in PTSD has recently been associated with structural brain atrophy in these patient cohorts (Chao, Weiner, & Neylan, 2013). Furthermore, **Study 2** demonstrated that hippocampus structure is strongly predictive of learning processes under the condition of sleep deprivation. PTSD patients commonly express co-occurring chronic sleep loss and memory impairment (Germain, 2013). Data from the current thesis supports the possibility that sleep deprivation in PTSD may (1) acutely modify hippocampal brain structure, and in turn, lead to (2) a shift in sleep spindle frequencies, and (3) a subsequent impairment in spindle-mediated discriminatory consolidation of memories based on salience and/or emotional relevance. If correct, such a predicted finding would motivate future studies to explore pharmacological (Göder et al., 2008) or non-pharmacological (Ngo, Martinetz, Born, & Mölle, 2013) interventions that targeting deficient spindle activity in PTSD, offering therapeutic sleep-dependent memory benefits as a consequence.

*ADHD:* Marked age- and puberty-dependent changes occur in NREM sleep physiology (Kurth et al., 2010), notably in slow waves. These changes have been proposed to reflect underlying development in neural white and grey matter (Buchmann et al., 2010). The mechanisms supporting these changes are relevant in contexts where development is abnormal, such as ADHD. Sleep disparities in ADHD may directly reflect changes in brain structure. For example, significant developmental delays in NREM slow wave activity over prefrontal cortex have been reported in ADHD (Ringli et al., 2013), occurring in parallel with similar deficits in the normative course of prefrontal grey matter development (Batty et al., 2010). Data from **Study 1** offer an explanatory framework intimating that these two symptoms of ADHD may be causally related. **Study 1** described a determinant relationship between frontal grey matter (specifically cingulate and orbital regions) grey matter and slow wave activity. The deficits in grey matter in ADHD children overlap with these same medial prefrontal regions (Batty et al., 2010). Therefore, one testable hypothesis stemming from **Study 1** is that deficits in slow wave activity in these children arise directly from structural abnormalities in these slow wave-predicting brain regions. Further, when considering the findings of **Study 2**—illustrating the structural determinants of sleep physiology may ultimately determine functional outcomes for learning—an additionally prediction is that sleep-dependent episodic memory deficits (Prehn-Kristensen et al., 2013) present in ADHD may arise from these underlying structural deficits. More broadly, regional brain structure offers one potential candidate factor linking parallel changes in sleep and cognition in disorders such ADHD. Detailed quantitative analysis of sleep electrophysiology of NREM sleep in ADHD, in combination with sleep-dependent hippocampal memory assessments and structural neuroimaging, will prove useful in more clearly discerning these relationships. Finally, such a framework offers the potential for therapeutic interventions, targeting the manipulation of slow wave activity (Marshall, Helgadóttir, et al., 2006) in this developmental ADHD cohort. By correcting slow wave activity to normal developmental levels, this manipulation may putatively aid in ameliorating the cognitive deficits present in ADHD.

Beyond PTSD and ADHD, these data support a broader mechanistic framework that may

causally unite co-morbid disruptions in brain function, sleep, and brain structure arising from neurological (e.g. narcolepsy (Joo, Tae, Kim, & Hong, 2009)), medical (e.g. sleep apnea (Weng et al., 2014)), psychiatric (e.g. major depression (Qiu et al., 2014)), and developmental (e.g. autism (Radulescu et al., 2013)) conditions.

## Future directions: Expanding upon mechanism

While these studies offer convergent structural indices explaining inter-individual differences in sleep physiology and associated individual differences in functional memory outcomes, the factor(s) that initially determine such structural brain differences, and with them, changes in sleep physiology and associated functions, warrant further exploration. One obvious potential candidate is trait genetics, for which there is preliminary data now beginning to emerge. For example, the PER3 tandem repeat polymorphism strongly moderates the expression of sleep EEG physiology (Viola, Archer, et al., 2007)—particularly slow waves. Moreover, the PER3 polymorphism has been reported to determine, in part, the vulnerability of cognition to sleep loss, specifically in the attentional domain (Rupp et al., 2013). While sleep and circadian regulatory genes, such as PER3, have yet to be linked to regional brain morphology, one hypothesis is that the stable associations established in the current thesis stem from underlying genotypic variability. Future studies targeting this question of offer a root-causal link from genes to brain structure, to sleep physiology and consequential sleep-dependent brain functions, and with it, direct translational disease and therapeutic relevance.

More generally, and when taken in the context of increasing curtailment of sleep in modern society (Czeisler, 2011), the trait-like nature of vulnerability of learning and memory function to sleep loss offers a powerful opportunity to predict which individuals may be most resilient to such conditions. This is especially relevant in circumstances and profession where insufficient sleep is common yet learning and memory functioning remains paramount, including the military, aviation, and medical and emergency service personnel (Czeisler, 2011). These thesis data, focusing on trait-like structural brain predictors of sleep-dependent physiology and associated cognition, offer one possible biomarker of relevance in these vulnerable occupational circumstances.

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