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Heart-brain Interaction during NREM Sleep Drives Sleep-dependent Memory Gains

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by

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Table of Contents

List of Figures

List of Tables

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Abstract of the Dissertation

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The last decade has seen significant progress in identifying sleep mechanisms that support cognition. Most of these studies focus on the link between electrophysiological events of the central nervous system during sleep and improvements in different cognitive domains, while the dynamic shifts of the autonomic nervous system across sleep have been largely overlooked. Recent studies, however, have identified significant contributions of autonomic inputs during sleep to cognition. Yet, there remain considerable gaps in understanding how central and autonomic systems work together during sleep to facilitate cognitive improvement. My dissertation work investigates the independent and interactive roles of central and autonomic activities during sleep and wake in cognitive processing. I specifically focus on the prefrontal-subcortical working memory (WM) processing and mechanisms underlying the formation of hippocampal-dependent episodic long-term memory (LTM). Here, I first present an introduction to heart-brain interaction and memory processing during sleep. Next, I show two experimental studies where I examine the role of autonomic activities and autonomic-central couplings during sleep on WM, which has

reliably been shown to benefit from sleep. Lastly, I present a pharmacological within-subjects, double-blind, placebo-controlled study that identifies separate and competing underlying mechanisms between autonomic and central activities supporting WM and LTM. In light of these three studies' novel contributions, I propose a theoretical model – the Sleep Oscillation Switch (SOS) Model that sleep is a competitive arena in which autonomic WM and LTM vie for limited resources.

Overview

One of the primary functions of sleep is to support cognition, however, the precise mechanisms are not fully understood. The majority of studies examining this question have focused on brain activity of the central nervous system, identifying specific, electrophysiological signatures of non-rapid eye movement (NREM) sleep, e.g. sleep spindles (12-15Hz) and slow oscillations (SOs, 0.5-1Hz), that are linked to sleep-related plasticity. Given that the transition from wake to sleep induces dramatic changes to both the central and autonomic nervous systems, a newer approach investigates whether autonomic features may also contribute to cognition. This emergent line of research examining brain-body communication suggests that autonomic activity may be linked with central brain activity during sleep, and that such heart-brain interaction facilitates both long-term episodic memory consolidation and short-term working memory processing during sleep. However, the mechanism by which the sleeping brain performs both of these complex feats and which sleep features are associated with these processes remain unclear. In this thesis, Chapter 1 includes an introduction on heart-brain interaction, namely the interaction between the autonomic and central nervous system, and their roles on memory processing during sleep. Chapters 2 and 3 cover my previous peer-reviewed work that examined the roles of autonomic activity and autonomic-central coupling during sleep on working memory (Chen, Whitehurst, et al., 2020a; Chen, Whitehurst, et al., 2020b). Finally, in Chapter 4, I present my recently published work demonstrating that long-term and working memory are served by distinct offline neural mechanisms during sleep, and that these mechanisms are mutually antagonistic. In Chapter 4, I further propose a Sleep Oscillation Switch (SOS) model in which the brain toggles between the two memory processes via a complex interaction at the synaptic, systems, and mechanistic level, with implications for research on cognitive disturbances observed in neurodegenerative disorders such as Alzheimer's and Parkinson's disease, both of which involve the decline of sleep.

Chapter One: An introduction to heart-brain interaction and memory processing during sleep

The Autonomic Nervous System: Connections and Measurements

The autonomic nervous system (ANS) is divided into two branches, with the sympathetic branch associated with energy mobilization during so-called fight-flight-freeze responses (Hagenaars et al., 2014; Miki & Yoshimoto, 2010), and the parasympathetic branch associated with vegetative and restorative functions during so-called rest-digest responses (Taylor et al., 2000). These branches "work antagonistically, synergistically, and independently to gather information from sensory organs and coordinate responses to internal and external demands" (Whitehurst et al., 2022). Both the sympathetic and parasympathetic nervous systems communicate with the central nervous system (CNS), forming a system named the central autonomic network (CAN). CAN is a set of CNS structures, including the locus coeruleus (LC), hypothalamus, amygdala, ventromedial prefrontal cortices (PFC), hippocampus, and thalamus, that, directly or indirectly, receive inputs from and modulate output to the ANS. The vagus nerve (the 10th cranial nerve) is comprised of approximately 80% afferent connections (see Breit et al., 2018 for a review) that communicate parasympathetic/vagal information from the periphery to the nucleus of the solitary tract (NTS) in the brainstem and higher-order CAN areas (Kalia & Sullivan, 1982; Sumal et al., 1983). Additionally, descending projections from CAN allow for bi-directional communications between the CNS and ANS (Shaffer et al., 2014; Thayer & Lane, 2009a).

In humans, a noninvasive method to detect ANS activity is heart rate variability (HRV), which examines the variability between individual R peaks (R-R intervals; reflecting ventricular depolarization) in the QRS complex of electrocardiogram (ECG) (Kleiger et al., 2005; Laborde et al.,

2017; Malik, 1996; Shaffer et al., 2014). HRV can be calculated in the time domain and the frequency domain. Time-domain measures of HRV include (a) the standard deviation of all R–R intervals (SDNN), a general measure of variability in heart rate; and (b) the root mean square of successive differences (RMSSD), a measure of heart rate fluctuations mediated primarily by the vagus nerve. Frequency-domain measures of HRV include (a) the power of high-frequency HRV (HF-HRV: 0.15-0.40Hz), an indicator of respiratory sinus arrhythmia and parasympathetic vagal activity; (b) the power of low-frequency HRV (LF-HRV: 0.04–0.15 Hz), a mixed-signal from both sympathetic and parasympathetic sources. Given the uncertainty in the contribution of signals comprising LF-HRV, relative to the known vagal origins of the HF-HRV signal, research on autonomic activity tends to focus on HF-HRV.

Autonomic inputs during wake modulate cognition

Cognitive processes that rely on top-down inhibitory control in prefrontal-subcortical networks, such as emotional regulation, cognitive control or executive function, have been associated with parasympathetic/vagal activity. Cognitive control or executive function, the coordination of mental processes and action in accordance with current goals and future plans, is a primary function of the prefrontal cortex (PFC). The coordination of cognitive control is implemented by multiple functional circuits anchored in the PFC, including the ventromedial prefrontal cortex, anterior cingulate cortex, and a wide range of subcortical regions (Menon & D'Esposito, 2021). WM is an aspect of executive function that supports the maintenance and manipulation of a small quantity of information, usually lasts seconds to minutes (Baddeley Alan, 1992), and shares similar neural mechanisms with cognitive control (Braver et al., 2007).

Parasympathetic/vagal activity is thought to be an indicator of the degree to which the prefrontal-subcortical circuit regulates its component systems in response to internal and external demands. Specifically, activity in these inhibitory circuits has been positively associated with

resting HF-HRV (Lane et al., 2009; Thayer & Lane, 2009a), and optimal functioning of these circuits is hypothesized to predict flexible and adaptive responses to environmental changes (Thayer et al., 2012). One prominent model aimed to explain how the bi-directional communication between CNS and ANS is a critical predictor of adaptive cognitive success is the Neurovisceral Integration Model, developed by Thayer and colleagues (Thayer & Lane, 2000, 2009; Figure 1.1). This model proposes that HRV is an index of prefrontal-subcortical inhibitory influence over a wide range of brain areas supporting cognition, emotion, and physiological reactivity, including executive function, WM, expectation of future outcomes, emotional regulation, emotional response to stress, as well as peripheral functioning (for review see Thayer et al., 2012).

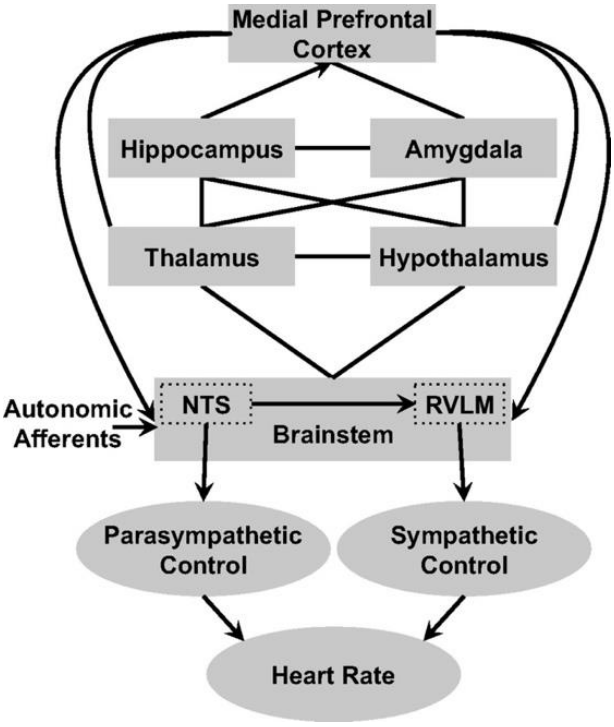


Figure 1.1 Connections Between Autonomic Centers and Higher-Order Cognition Areas

Bidirectional innervations between peripheral organs, including the heart, and the central nervous system, beginning at the brainstem, link brain areas associated with cognitive processing to brain areas controlling heart rate and HRV. In this figure, lines denote bidirectional connections and arrows denote mono-directional projections. Note that for clarity, not all areas are reported in the current figure. Reprinted from Whitehurst et al., 2016.

The Neurovisceral Integration Model gained empirical support from studies showing the relationship between HRV during wakefulness and executive function. Compared to individuals with low resting HF-HRV (reflecting poor parasympathetic vagal tone during awake rest), high HF-

HRV individuals show better WM performance (n-back task: Hansen et al., 2003; operation-span task: Mosley et al., 2018), and inhibitory control (i.e. Stroop task; Hansen et al., 2004). In addition, training-induced changes in cognitive control are associated with improvements in parasympathetic activity, and the reversal is also true that training-induced increases in parasympathetic activity also promote cognitive enhancement. For example, cognitive training (vision-based speed of processing) has been shown to increase HF-HRV and enhance activation in the prefrontal-subcortical network (Lin, L Heffner, et al., 2017). In this study, older adults with amnestic mild cognitive impairment underwent six weeks of cognitive training. Compared to controls, older adults in the active training group demonstrated increased HF-HRV and decreased prefrontal-striatal connectivity during the task, suggesting an efficient prefrontal-subcortical autonomic regulation. Similar results were reported in healthy participants (Xiu et al., 2016). Furthermore, increasing resting HF-HRV via aerobic training has been reported to parallel improvements in WM performance (Hansen et al., 2004). In this study, participants were randomly assigned to an aerobic training group and a detraining group (reduced exercise condition), with resting HF-HRV and WM measured before and after the exercise intervention. Post-intervention, the aerobic training group showed greater HF-HRV and WM performance compared to the detraining control group, suggesting a link between the strengthening of parasympathetic/vagal functioning and WM networks via cardiac exercise.

How might vagal/ parasympathetic activity benefit WM? One mechanism is through increasing NE. Despite the traditional assumptions that the vagus nerve only modulate activity in the ANS, and that vagal activity only affects ACh but not NE, the last 20 years of research has demonstrated that the vagal afferents modulate NE levels in the brain. The vagus nerve represents the main component of the parasympathetic nervous system, and activating ascending fibers of the vagus nerve mediate NE's actions on the brain (McIntyre et al., 2012; Miyashita & Williams, 2006). The terminals of the afferent vagus nerve transmission are directly within the nucleus tractus

solitarii (NTS). After activation by vagal afferents, NTS neurons convey information to structures that regulate higher-order cognition such as the amygdala, hippocampus, and frontal cortex via a polysynaptic pathway to the LC. Although ACh is the primary neurotransmitters in the peripheral synapses of the vagus nerve, once the information propogate to the LC, NE becomes the primary transmitters to mediate synaptic communication in the central nervous system.

It is crucial to distinguish the effects of phasic and tonic LC-NE neuron firings. Tonic LC-NE activation has been linked to stress or arousal, whereas phasic NE has been linked to responses to novelty and higher-order cognition (Ross & Van Bockstaele, 2021). Phasic and tonic activations are antagonistic, with phasic activity optimized when moderate level of tonic activity (Aston-Jones & Cohen, 2005), while elevated tonic discharge can impair phasic discharge (Janitzky, 2020). In primates, phasic activation of NE neurons of the locus coeruleus in time with cognitive shifts could provoke or facilitate dynamic reorganization of target neural networks, permitting rapid behavioral adaptation to changing environmental imperatives (Bouret & Sara, 2005). Furthermore, it has been recently shown that phasic-LC optogenetic activation of locus coeruleus protects against deleterious human pretangle tau effects and cognitive decline, while stress-inducing tonic-LC activation worsens its effects (Mather & Harley, 2016; Omoluabi et al., 2021). Specifically, in the study conducted by Omoluabi and colleagues (2021), mice were injected with pretangled tau and their LC neurons were activated in either phasic or tonic patterns. They found that phasic stimulation rescued mice from behavioral and LC deficits, while tonic stimulation led to worsened symptoms (Omoluabi et al., 2021).

In humans, a causal link between vagal inputs modulating LC-NE activity and cognitive domains supported by the PFC has been established by studies actively manipulating vagal tone using vagal nerve stimulation (VNS) or non-invasive transcutaneous vagus nerve stimulation (tVNS). VNS activates phasic neuron firings in the LC and increases norepinephrine (NE) levels in

the prefrontal-subcortical networks, including the neocortex, hippocampus, amygdala, and other parts of the brain with afferent projections from LC (Hassert et al., 2004; Hulsey et al., 2017; Janitzky, 2020; Raedt et al., 2011). In one study, patients treated with invasive VNS performed cognitive tasks with stimulation on or off. Patients demonstrated improved WM performance during the stimulation-on periods compared to the stimulation-off periods (Sun et al., 2017). More recently, non-invasive transcutaneous vagus nerve stimulation (tVNS) has shown similar effects to cognitive control (Pihlaja et al., 2020). In this study, healthy participants performed a Go/NoGo task with active tVNS or sham stimulation. In the NoGo condition, tVNS resulted in significantly reduced amplitude of frontal N2 event-related potentials, a biomarker for demanding cognitive control, suggesting that tVNS may lead to more efficient neural processing with fewer resources needed with successful frontal inhibitory control. Similar effects of tVNS have been demonstrated in another study (Keute et al., 2020) in which tVNS increased frontal midline theta activity, thought to reflect transient activation of the PFC in situations requiring increased executive control of actions.

Along with electrical stimulation of the vagus nerve, another strong modulator of parasympathetic/vagal activity is the sleep/wake cycle. Recent studies have demonstrated a potential link between the natural amplification of the parasympathetic system during sleep with WM function. The next section will review findings on the relationship between sleep and ANS activity.

Sleep modulates heart-brain interactions

The transition from wake to sleep produces the largest shift in autonomic activity we experience every day. Sleep is not one uniform event, and its characterization into organized stages shows specific profiles in central and autonomic activity during each stage. Over a night of sleep, the human brain cycles through two primary phases: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further divided into stage 1, 2, and 3 (or slow-wave

sleep) (Iber et al., 2007). Stage 1 sleep is a transitional state from wake to sleep, making up 3% of adult nocturnal sleep. About 60% of adult sleep is stage 2 sleep, which is marked by distinct electrophysiological events named sleep spindles and K-complexes. Stage 3, or slow-wave sleep (SWS), makes up about 20% of sleep, and it is marked by slow, high-amplitude oscillations called slow oscillations (SOs, <1Hz) and slow-wave activity (SWA, 0.5-2Hz). In NREM sleep, cholinergic systems in the brainstem and forebrain become markedly less active; firing rates of LC-NE and serotonergic Raphé neurons are also reduced, compared to waking levels (Saper et al., 2001). However, the conventional dogma about the relative quiescence of LC-NE neurons during NREM sleep has been challenged by evidence of a transient increase in LC-NE activity during NREM sleep (Eschenko & Sara, 2008). A simultaneous EEG-fMRI study in humans further revealed that the increased activity of the LC nucleus is temporally related to SO down-to-up transitions (Dang-Vu et al., 2008; Eschenko et al., 2012), suggesting a more complex neuromodulator dynamics during NREM sleep. Activity of LC-NE neurons during NREM sleep is potentially relevant in understanding how autonomic activity during this sleep period may contribute to cognitive enhancement. After a bout of SWS, the brain shifts into REM sleep, which makes up about 20% of human sleep and it is marked by sudden bursts of eye movements and faster, low-amplitude alpha (8-12Hz) and theta (4-8Hz) oscillations. During REM sleep, both aminergic populations are strongly inhibited, while cholinergic systems become more active compared to waking levels (Marrosu et al., 1995). The transition through stage 2, SWS, and REM occurs in 90-100 minutes cycles across the night, with the first half of the night dominated by SWS and the second half of the night dominated by REM sleep (Plihal & Born, 1997)

In peripheral sites, the transition from wake to SWS is associated with a significant drop in heart rate and blood pressure, as well as increased dominance of HF HRV (Bušek et al., 2005; Tobaldini et al., 2013). The blood pressure plunge during NREM sleep compared to wake is beneficial for cardiovascular health, leading some experts to describe sleep as a “cardiovascular

holiday" (Trinder et al., 2012). SWS, in particular, is a period of cardiovascular quiescence and may represent an opportunity for the cardiovascular system to recuperate from daytime insults, such as stress-induced blood pressure surges. Indeed, one study comparing amounts of SWS and subclinical markers of cardiovascular disease (CVD) found that participants who experienced greater SWS showed lower markers of CVD after cardiovascular stress (Brindle et al., 2018), suggesting that SWS may buffer autonomic responses to daytime stress that may modify disease risk.

Additionally, sleep, rather than circadian effects, appears to influence ANS activity, as similar HRV profiles have been shown in daytime and nighttime sleep (Whitehurst et al., 2018), which may also indicate that daytime naps serve as a mini-cardiovascular holiday. Furthermore, a study comparing HRV profiles during a 50-min nap versus waking rest in supine position reported parasympathetic dominance during sleep only, and not during quiet rest, indicating that the cardiovascular benefits are specific to sleep (Chen et al., 2021).

Studies have revealed a consistent interdependency between the heart and brain activity, with temporally coincident changes in EEG delta (0.5-4Hz) power and ANS activity (Ako et al., 2003; Brandenberger et al., 2001a; Kuo & Yang, 2004; Rothenberger et al., 2015; Thomas et al., 2014; Yang et al., 2002). In fact, modulations in HRV are so closely associated with the onset of SWS that they can be used as a parameter to automatically detect SWS (Shinar et al., 2006). Furthermore, delta band power, a marker of homeostatic sleep drive that dissipates across successive NREM periods, shows inverse coupling with LF/(LF+HF) ratio during nighttime sleep. Generally, the LF/(LF+HF) ratio increases during REM sleep and decreases during SWS (Figure 1.2a, Brandenberger et al., 2001), indicating greater sympathetic activity during REM sleep, with heart rate and blood pressure levels reaching values similar to wake (Trinder et al., 2001). In fact, parasympathetic/vagal activity during NREM sleep and sympathetic activity during REM sleep can exceed average levels of quiet wakefulness (Trinder et al., 2001). Figure 1.2b demonstrates the power spectrum of RR-intervals during quiet wake, stage 2, SWS and REM sleep (Figure 1.2b, Naji

et al., 2019b). More recently, causally increased SWA via acoustic SOs stimulation resulted in increased vagal activity (measured by HF-HRV and SDNN) during SWS compared to sham stimulation (Diep et al., 2022), suggesting a strong interdependency between vagal activity and slow EEG oscillatory events during SWS.

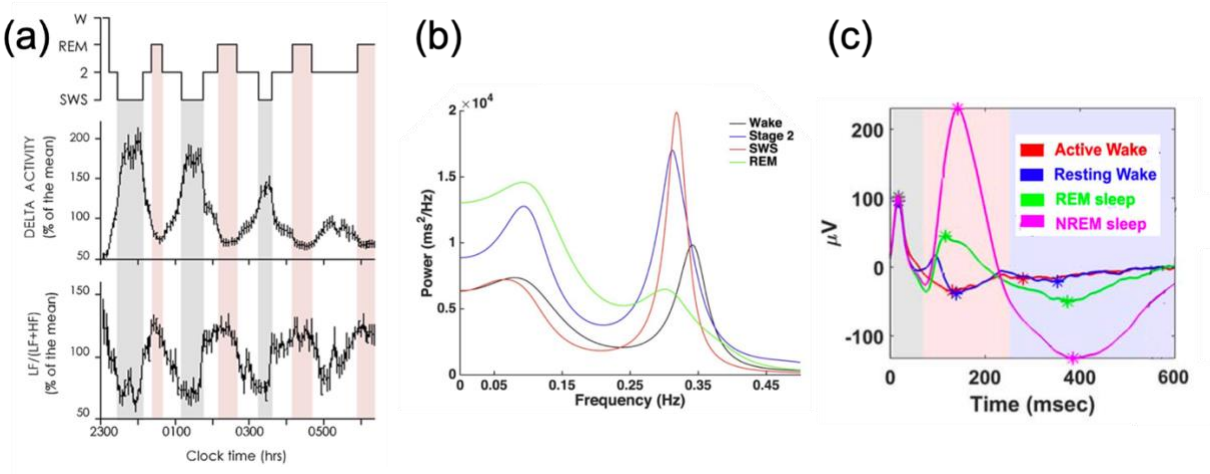


Figure 1.2 Vagal activity is boosted during SWS

(a) Delta wave activity and LF/(LF+HF) ratio with a hypnogram during nighttime sleep. Reprinted from Brandenberger et al. 2001. (b) RR power spectrum modulated by sleep stages. NREM Stage 2 and SWS demonstrate greater parasympathetic activity indexed by HF-HRV, compared to REM sleep and Wake. Reprinted from Naji et al., 2019b. (c) Vagal-evoked potentials (VEPs) in the macaque monkey brains by sleep stages. NREM sleep demonstrated 300-500% greater VEPs , compared to REM sleep and Wake. Reprinted from Rembado et al., 2021.

Considering more temporally precise levels of analysis, coupling has been shown between individual ANS and CNS events, such as heartbeats and EEG SOs in deep sleep (Lechinger et al., 2015). Using a cross-correlation approach, Thomas et al. (2014) showed a temporal relation between SWA and high frequency cardiopulmonary (0.1-0.4Hz) coupling, an ECG-derived biomarker of stable sleep, during NREM sleep. Several studies have also reported on coupling between autonomic and central events (ACEs) whereby short bursts of heart rate are temporally coincident with transient increases in SOs during NREM sleep (Chen, Whitehurst, Naji, et al., 2020b; Naji et al., 2019). Rembado and colleagues recorded vagal-evoked potentials (VEPs), manifested as

the vagal afferents to the cerebral cortex in responses to VNS, in the macaque monkey brains during different consciousness states (Rembado et al., 2021). VEPs were reported to be 300-500% larger during NREM sleep, compared to REM sleep and wakefulness (Figure 1.2c, Rembado et al., 2021), and critically, VEPs during NREM were larger for stimuli delivered at the depolarized phase of ongoing delta oscillations, suggesting a close temporal coupling between ANS and CNS events. These findings demonstrate that CNS-ANS dynamics support the interdependency between cortical and cardiac function during sleep. Moreover, taken together with findings from wake HRV studies, natural surges in parasympathetic activity during SWS suggest that HRV profiles during sleep might account for some degree of cognitive enhancement.

Sleep-dependent working memory improvements

Compared to wakefulness, sleep between WM training sessions may be critical for enhancing WM performance (Chen, Whitehurst, Naji, et al., 2020a; Kuriyama et al., 2008a; Lau et al., 2015a; MacDonald et al., 2018; Zinke et al., 2018a), potentially due to the effect of SOs (Ferrarelli et al., 2019; Pugin et al., 2015; Sattari et al., 2019; Figure 1.3). Moreover, a recent study using acoustic SO stimulation during nighttime sleep reported that stimulation improved WM as a result of enhanced SWA, compared to individuals whose SWA was not enhanced (Diep et al., 2020). Not all studies, however, find a positive association between EEG features of SWS and WM improvement (MacDonald et al. 2018; Chen et al., 2020). One potential reason for the lack of consistent findings may in part be related to the fact that few studies measure ANS activity during sleep and therefore miss the ANS's contribution to the performance change. My works in chapter two and three will demonstrate that along with EEG events of SWS, naturally elevated vagal activity and autonomic-central coupling during SWS also supports WM improvement in young adults.

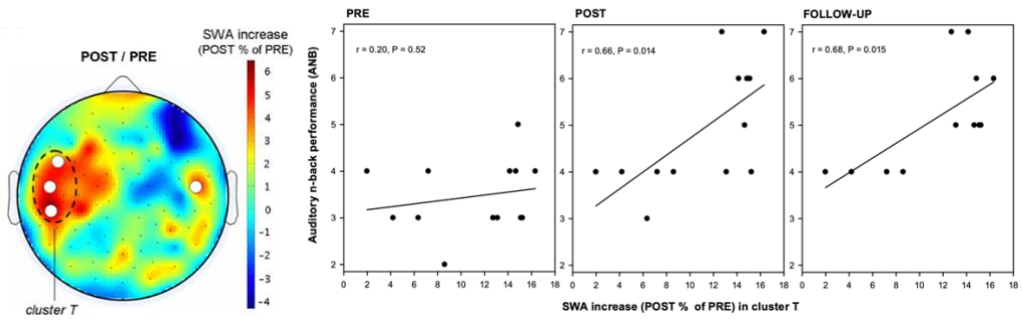


Figure 1.3 SWA during SWS associated with WM improvement
Three weeks of WM training increased SWA during sleep, which correlated with WM performance post-training. Reprinted from Pugin et al. 2015.

We now turn to the question of LTM, for which ample evidence supports a role of SWS specifically in consolidation of hippocampal-dependent episodic memories. And yet, evidence for a potential role of ANS activity during sleep in this process remains scarce, a gap that may in fact have explanatory value.

Sleep-dependent long-term memory consolidation

Hippocampal-dependent, episodic long-term memory refers to the conscious recollection of information specific to the time and place of acquisition (Moscovitch et al., 2016). A growing literature supports the role of sleep in the consolidation of episodic memories and has identified a critical role for specific electrophysiological events during NREM sleep (see Diekelmann & Born, 2010 for a review). Although there is much debate as to how recent experiences are represented and transformed in cortical and subcortical long-term stores (Nadel & Moscovitch, 1997; Sekeres et al., 2018; Yonelinas et al., 2019), there is a general consensus that the hippocampus is a fast-learning system that binds recent experiences into representations across different cortical structures during encoding (Ekstrom & Yonelinas, 2020). During consolidation, repeated reactivation stabilizes and strengthens memory traces, with sleep being an optimal offline period

for consolidation as it facilitates the dialogue between the hippocampus and the neocortex (Rasch & Born, 2013). Specifically, during NREM sleep, the memory trace is reactivated by hippocampal sharp-wave ripples (SPW-R) nested within thalamic spindles, which are in turn nested within the down-to-up transition of the SO, providing a pathway for neural communication between neocortical and hippocampal cell assemblies. Spindles have recently been recognized as playing a causal role in hippocampal-dependent memory consolidation via pharmacology studies (Mednick et al., 2013; Zhang et al., 2020) and studies using targeted memory reactivation (Antony et al., 2018; Cairney et al., 2018). Mednick and colleagues compared zolpidem, a short-acting GABA-A agonist, with placebo and a positive control hypnotic (sodium oxybate) across a night of sleep. Compared with controls, zolpidem increased sleep spindles and enhanced hippocampal-dependent, episodic verbal memory, and the spindle boost mediated the memory improvements. Several other pharmacology studies have corroborated these findings (Wamsley et al., 2013; Zhang et al., 2020), implicating GABAergic modulations of the thalamocortical network as important for LTM formation.

Despite the growing list of studies demonstrating a role for ANS activity in executive function and WM, links to LTM are sparsely reported, and no studies have endorsed a role for ANS during sleep in hippocampal-dependent episodic LTM specifically. One study showed that overnight improvement in non-hippocampal-dependent procedural memory was correlated with LF-HRV and SDNN during sleep (van Schalkwijk et al., 2019). In addition, parasympathetic activity (HF-HRV) during REM sleep strongly predicted improvement in implicit priming in a creativity task (Whitehurst et al., 2016). Studies examining the impact of HRV during wakefulness on episodic LTM also show mixed results. One study demonstrated that people with poor vagal autonomic functioning (low resting HRV) show greater false memory errors (Feeling et al., 2021). In addition, cardiac vagal tone has been shown to positively correlate with better memory for emotionally-charged stimuli (Mattarozzi et al., 2019; Wendt et al., 2019), albeit no relation with memory for

neutral stimuli. In contrast, several studies showed that HRV during wakefulness does not predict episodic memory performance (Aguillard et al., 2020; Paige et al., 2020; Zeki Al Hazzouri et al., 2018). Taken together, the emerging picture of the role of CNS and ANS inputs for cognitive enhancement is that SWS is an optimal brain state for the stabilization of episodic, long-term, non-emotional memories, as well as for the improvement of executive function, but not necessarily via the same mechanisms.

Working and long-term memory interaction during sleep

While studies have shown that both SWS (including SWA and SOs) and vagal activity during SWS contributes to WM, and that SO-spindle-ripple complexes contribute to episodic LTM, the relation between WM and episodic LTM remains unclear. On one hand, studies have shown positive associations between WM and LTM, such that WM increases LTM recognition and WM capacity constrains LTM encoding (Cotton & Ricker, 2021; Forsberg et al., 2021). On the other hand, Hoskin and colleagues (2019) demonstrated that episodic memory reactivation during wake intrudes on WM maintenance (Hoskin et al., 2019), suggesting coordinated activity patterns across a broad swath of cortical regions, including the PFC, triggered by memory reactivation may steal resources from WM maintenance. Thus, WM and episodic memory may be supported by separate and potentially competitive, neural mechanisms, namely, the LC-NE prefrontal-subcortical network and the GABAergic thalamocortical hippocampal network, respectively.

At the neuromodulatory level, along with LC-NE enhancement of WM (VNS studies), animal studies have implicated this system during and immediately following encoding novel experiences (Kobayashi & Yasoshima, 2001; McGaugh, 2013), and in wake-dependent gene expression regulating synaptic potentiation that supports learning (Tully & Bolshakov, 2010). However, while reversible inactivation of LC during the Morris water maze task demonstrated significant

impairments in spatial memory encoding and WM, consolidation and retention of spatial memory were not affected (Khakpour-Taleghani et al., 2009). Together, these findings suggest that the LC-NE system may play an important role in early acquisition of new experiences and in cognitive control efficiency, but not in consolidation and retrieval of LTM.

In humans, recent findings in the tVNS literature have corroborated a selective functional role of the LC-NE system in cognitive control, but not in LTM. A meta-analyses on 19 tVNS studies (Ridgewell et al., 2021) showed significant effects of acute tVNS on cognitive inhibitory control, particularly as task difficulty increases, but no evidence supporting the effectiveness of tVNS on LTM performance, attention, or other cognitive domains. Specifically, Mertens and colleagues (2020) found that tVNS had no effect on either immediate or delayed word recognition memory in young and middle-aged adults (Mertens et al., 2020). Furthermore, Lozano-Soldevilla and colleagues (2014) administered a GABAergic benzodiazepine (lorazepam) to healthy adults and reported dose-dependent decreases in WM (Lozano-Soldevilla et al., 2014), suggesting an antagonistic relation between GABA and LC-NE prefrontal-subcortical networks.

Competition between these networks may be especially prevalent during offline sleep (Gervasoni et al., 1998; Logothetis et al., 2012; Novitskaya et al., 2016). Gervasoni and colleagues applied a GABA-A antagonist during SWS in rats and reported restoration of tonic firing in the LC-NE neurons, which are typically suppressed during SWS compared to wakefulness (Gervasoni et al., 1998). Furthermore, during hippocampal ripples, signatures of LTM replay and consolidation, Logothetis and colleagues demonstrated deactivations in brainstem regions regulating the ANS. These fascinating results may mean that during sleep-dependent memory consolidation, ripple/spindle complexes may orchestrate a privileged interaction state between hippocampus and cortex by silencing the output from diencephalic, midbrain, and brainstem regions (Logothetis et al., 2012). Interestingly, the deactivation of the basal ganglia, the pontine region and the cerebellar cortex, is consistent with prior evidence of competition between episodic and procedural memory

systems (Poldrack & Rodriguez, 2004). In the reverse direction, Novitskaya and colleagues (2016) experimentally increased NE by LC stimulation and blocked the generation of ripple-associated cortical spindles, thus interfering with spatial LTM consolidation (Novitskaya et al., 2016). Moreover, Marzo and colleagues (2014) have shown that electrical stimulation of LC transiently suppressed SOs and spindles in the anesthetized rodent (Marzo et al., 2014). It is also well documented that NE input shifts the thalamo-cortical network from a synchronized state associated with SOs and spindles to a desynchronized state characterized by increased neuronal responsiveness to synaptic inputs, which is more optimal for encoding and sensory processing (McCormick, 1989).

Chapter Two: The role of autonomic activities during sleep on working memory improvement

Abstract

Recent investigations have implicated the parasympathetic branch of the autonomic nervous system in higher-order executive functions. These actions are purported to occur through autonomic nervous system's modulation of the PFC, with parasympathetic activity during wake associated with working memory (WM) ability. Compared with wake, sleep is a period with substantially greater parasympathetic tone. Recent work has reported that sleep may also contribute to improvement in WM. Here, we examined the role of cardiac parasympathetic activity during sleep on WM improvement in healthy young adults. Participants were tested in an operation span task in the morning and evening, and during the intertest period, participants experienced either a nap or wake. We measured high-frequency heart rate variability as an index of cardiac, parasympathetic activity during both wake and sleep. Participants showed the expected boost in parasympathetic activity during nap, compared with wake. Furthermore, parasympathetic activity during sleep, but not wake, was significantly correlated with WM improvement. Together, these results indicate that the natural boost in parasympathetic activity during sleep may benefit gains in prefrontal executive function in young adults. We present a conceptual model illustrating the interaction between sleep, autonomic activity, and prefrontal brain function and highlight open research questions that will facilitate understanding of the factors that contribute to executive abilities in young adults as well as in cognitive aging.

Introduction

Working memory (WM), the ability to retain, manipulate, and update information over

short periods of time for use in top-down control of complex cognitive tasks, is essential to higher order cognition and to performance of daily activities. According to the WM model by Baddeley & Hitch (Baddeley & Hitch, 1974), it comprises a verbal and visuospatial system, which are both controlled by an executive system. With these subsystems, WM has been shown to support a wide range of complex cognitive functions, including logical reasoning and problem solving, and related to measures of fluid intelligence (Conway et al., 2002; Engle et al., 1999). These abilities are mediated primarily by the prefrontal cortex interacting with striatal and hippocampal areas (Miller & Cohen, 2001). Decades of work have shown strong neural activity in PFC when performing WM tasks (Funahashi et al., 1993; Fuster & Alexander, 1971; Levy & Goldman-Rakic, 2000). From an aging perspective, WM functions are prone to age-related cognitive decline. This decline is already evident in the normal aging process but is particularly pronounced in old-old (age > 75) adults (Hale et al., 2011). Considering the importance of WM for cognitive functions, the question of possibly modifying WM decline has been raised. Illuminating the mechanisms of WM improvement is important as this domain has been the focus of cognitive training in older adult populations with the expectation that enhanced WM will generalize to a wide range of cognitive functions and potentially slow the speed of cognitive aging.

WM training typically requires practice over a span of days, weeks or months, suggesting that offline, sleep-dependent mechanisms may be involve in the long-term improvement of WM. Sleep plays an important role in the maintenance and improvement of a wide range of cognitive processes, including the consolidation of declarative memory and procedural memory, as well as maintaining executive function, including sustained attention and WM (Könen, Dirk, & Schmiedek, 2015; Vriend et al., 2013). Indeed, it's known that sleep deprivation/restriction detrimentally affects WM. For example, sleep deprivation/restriction lead to impairment in sustained attention (Goel et al., 2009; Lo et al., 2012) and a variety of cognitive tasks involving WM, such as digit span. (Quigley, Green, Morgan, Idzikowski, & King, 2000) and N-back tasks (Choo, Lee, Venkatraman,

Sheu, & Chee, 2005), effects likely driven, in part, by altered functioning of frontal and parietal networks (Chee & Choo, 2004). Although studies have repeatedly demonstrated that a sleep-deprived brain, compared with a well-rested one, performs worse on WM tasks (Lo et al., 2012; 2016), much less is known about the direct contribution of sleep-specific mechanisms supporting WM improvement. Recently, studies that directly tested the effect of post-training sleep on WM performance suggested that a period of sleep, compared to wake, facilitates WM. (Zinke et al., 2018b; Kuriyama et al., 2008b; Lau et al., 2015b). In these studies, training adult participants on an N-back task over several sessions improved accuracy of performance, but only if the interval between training sessions included nocturnal sleep (Zinke et al., 2018b; Kuriyama et al., 2008b) or a nap (Lau et al., 2015b), in comparison with daytime periods of wakefulness. One plausible neurophysiological mechanism for such training improvement is slow wave sleep (SWS). SWS has received increasing attention due to its roles in offline memory consolidation and memory reactivation (Berkers et al., 2018; Marshall & Born, 2007). In addition, SWS has been linked to synaptic plasticity and cortical reorganization (Tononi and Cirelli, 2003; Takashima et al., 2006; Dang-Vu et al., 2010). Intriguingly, several studies have shown a specific association between electrophysiological (EEG) activity during SWS in the enhancement of WM. Pugin and colleagues (2015) demonstrated a correlation between SWA during SWS in frontal areas and WM performance after three weeks of WM training (Pugin et al., 2015). Furthermore, SWA during SWS has been shown to predicted WM gains across a period of sleep in both young (Ferrarelli et al., 2019) and older adults (Sattari et al., 2019). Taken together, these studies suggest that SWS might provide an optimal brain state for the improvement of WM.

A different line of research has demonstrated a significant contribution of the autonomic nervous system (ANS) for WM. Cardiac vagal tone, which represents the contribution of the parasympathetic nervous system to cardiac regulation is known for its role in regulating involuntary bodily functions, such as breathing, heart rate and digestion, and is less recognized for

its role in influencing cognitive processing. Yet, over recent decades, vagal activity is acknowledged to be linked with self-regulation at the cognitive, emotional, social, and health levels. Thayer and others have published a body of research implicating cardiac vagal influence on a range of cognitive abilities supported by the prefrontal cortex (PFC) (Lane et al., 2001; Smith et al., 2017; Thayer & Lane, 2009b). Descending projections from the PFC to the brainstem and hypothalamic structures allow for bi-directional communication between the central nervous system and the ANS through the vagus nerve (Packard et al., 1995; Thayer et al., 2009), and thus prominent models of ANS and cognition, including the Neurovisceral Integration Model (Smith et al., 2017; Thayer & Lane, 2009b), have focused on the impact of vagal cardiac activity on executive function cognition. In humans, a well-established method to non-invasively examine autonomic activity is heart rate variability (HRV), which measures systematic variation in the beat-to-beat interval (Shaffer et al., 2014). The most commonly used HRV analytical approaches are time domain analysis and frequency domain analysis. The primary time domain measure is the root mean square of successive differences (RMSSD), which reflects the beat-to-beat variance in heart rate and is used to estimate vagally-mediated changes in the RR time series (Laborde et al., 2017; Shaffer et al., 2014). For frequency domain analysis, spectral analysis of the cardiac signal in the high frequency range (HF HRV: 0.15-0.40 Hz) is indicative of vagally-mediated respiration and parasympathetic cardiac activity. Vagally-mediated HRV (e.g. RMSSD, HF HRV) during wake has been shown to predict performance on a wide range of cognitive tasks that rely on PFC activity (Thayer et al., 2009). For example, compared to individuals with low resting vagally-mediated HRV, high HRV individuals perform better on both WM (n-back task: Hansen et al., 2003; operation-span task: Mosley et al., 2018) and cognitive inhibition (i.e. Stroop task; Hansen et al. 2004). Additionally, reducing HRV, via aerobic de-training, comes at significant cost to executive functioning (Hansen et al., 2004). More recently, studies have demonstrated that directly stimulating the vagus nerve can increase vagally-mediated HRV (Clancy et al., 2014), improve verbal memory (Clark et al., 1999; Jacobs et al., 2015),

and accelerate extinction learning (Burger et al., 2016). These studies suggest that strong modulation of ANS activity may benefit prefrontal functioning.

Sleep strongly modulates ANS activity (Baharav et al., 1995). As the brain shifts from wake into sleep, the body also undergoes marked changes with heart rate deceleration and relative increases in parasympathetic HF HRV across the three stages of non-rapid eye movement (NREM) sleep (i.e., Stage 1, Stage 2, and Slow Wave Sleep (SWS)) (Trinder et al., 2001). Additionally, similar HRV profiles have been shown between daytime (naps) and nighttime sleep (Cellini et al., 2016; Whitehurst et al., 2018). It is not known whether naturally elevated vagal activity during NREM sleep might support WM.

We investigated the impact of parasympathetic activity during sleep versus wake on both general WM performance (baseline at Test 1) and WM improvement across a day (difference score between Test 2-Test 1). We examined WM using the Operation Span Task (OSpan), which is a dual-task consisting of a processing subtask and a short-term memory subtask that has been commonly used to test central constructs of WM, but has not been examined in the context of sleep. Thus, the current study aimed: (1) to assess the cardiac activity across sleep stages during a daytime nap in healthy young adults; (2) to compare the effect of a daytime nap versus wake on WM improvement; and (3) to explore the impact of parasympathetic activity during sleep and wake on WM. We hypothesized that participants would show increases in parasympathetic activity during NREM sleep compared to waking and REM sleep. Furthermore, we predicted that sleep, especially SWS, would benefit WM to a greater extent than wake, and that parasympathetic activity during SWS would be positively associated with WM improvement to a greater extent than waking activity.

Methods

Participants

104 young adults (Age:17-23 [Mean=20.7, SD= 2.95], 60 males) with no personal history of neurological, psychological, or other chronic illness provided informed consent, which was approved by the University of California, Riverside Human Research Review Board. For participants under the age of 18 years, informed consent was obtained from a parent and/or legal guardian. All methods were performed in accordance with the relevant guidelines and regulations. Participants were randomized to either have a 2-hour nap opportunity monitored with polysomnography (PSG) (Nap, n=53), or stay awake (Wake, n=51), where subjects engaged normal daily activities with activity watch monitoring, but were not allowed to have caffeine or take a nap. Participants included in the study had a regular sleep-wake schedule (reporting a habitual time in bed of about 7–9 h per night), and no presence or history of sleep, psychiatric, cardiovascular, or neurological disorder determined during an in-person, online, or telephone interview. Participants received monetary compensation for participating in the study.

Working Memory Task

The current study used the Operation Span Task (OSpan)66 as a measure of WM capacity, which requires participants to solve a series of math operations while memorizing a set of unrelated letters. The task was programmed in Matlab (The MathWorks Inc., 2015) using Psychtoolbox, which allows random generation of stimuli every trial. The task included 3 practice and 40 test trials. Participants were tested in letter strings four and seven. For each letter string, participants were shown a series of math problems that they had to confirm were correct within 3 seconds, using pre-determined responses on the keyboard. After each equation, a letter would appear on the screen and the subject was instructed to remember each letter. At the end of each string, the participant was instructed to recall the letters in the order presented by typing responses on a computer keyboard. Immediately after each trial, the next letter string would be presented. An example of a four-item trial might be: 12 - 2 = 8 (correct/ incorrect?) >> J; 6 + 7 = 14

(correct/incorrect?) >> G; 3 - 2 = 1 (correct/incorrect?) >> S; 5 + 7 = 13 (correct/incorrect?) >> K. After verifying the four equations in this example, participants were asked to type the presented letters in the order that they were presented (in this case JGSK). If the participants forgot one of the letters in a trial, they were instructed to provide their best guess. In addition, to decrease trade-off between solving the operations and remembering the letters, a 70% accuracy criterion on the math operations was required for all the participants. We excluded 1 participant in the Nap group based on this criterion. We calculated performance as: number of correct letters recalled/ total number of letters in the string per trial, and then we averaged over the total 40 trials. For assessing change in performance from session 1 and session 2, we calculated the difference in performance between the two sessions (session 2 – session 1).

Study Procedure

Participants were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. Participants filled out sleep diaries for one week prior to the experiment and wore wrist-based activity monitors the night before the study (Actiwatch Spectrum, Philips Respironics, Bend, OR, USA) to ensure participants were well-rested (at least 7 hours per night for the youngers and 6 hours for the elders during the week including the eve of the experimental day). On the experimental day, participants arrived at the Sleep and Cognition lab at 10:00AM and had EEG electrodes applied, followed by an Operation Span (OSpan) WM task. Nap/wake interventions occurred between 1:30-3:30 PM. At 1:30PM, Nap subjects took a polysomnographically-recorded nap and were given 2-hours time-in-bed to obtain up to 90-min total sleep time. Sleep was monitored online by a trained sleep technician. In the wake group, subjects were asked not to nap, exercise, or consume caffeine or alcohol, and were monitored with actigraphy during the break. In addition, the EEG/ECG was not recorded during wake break. Between 4 and 4:30PM, all subjects were retested on the memory task. Subjects completed the

Karolinska Sleepiness Scale (KSS; T Åkerstedt, 1990) questionnaire two times throughout the experimental day; at the start of each WM task (Session 1 and Session 2) to report their sleepiness. KSS is a 9-point Likert scale often used when conducting studies involving self-reported, subjective assessment of an individual's level of drowsiness at the time, in which a higher score yields a sleepier state at that time.

Sleep Recording and Scoring

EEG data were acquired using a 32-channel cap (EASYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10-20 System31. 22 out of 32 electrodes were active scalp recordings. The remaining electrodes were used for electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), ground, an online common reference channel (at FCz location, retained after re-referencing), and mastoid (A1 & A2) recordings. The EEG was recorded with a 1000 Hz sampling rate, amplified (ActiCHamp), and was re-referenced to the contralateral mastoid (A1 & A2) post-recording. Only eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2), the EMG and EOG were used in the scoring of the nighttime sleep data. High pass filters were set at .3 Hz and low pass filters at 35 Hz for EEG, EOG and EMG. Raw data were visually scored in 30-sec epochs into Wake, Stage 1, Stage 2, Slow Wave Sleep (SWS; Stages 3 and 4) and rapid eye movement sleep (REM) according to the Rechtschaffen & Kales' manual using HUME, a custom MATLAB toolbox. Prior to sleep scoring, data were pre-processed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany).

Heart Rate Variability

Electrocardiogram (ECG) data were acquired at a 1000-Hz sampling rate using a modified Lead II Einthoven configuration. We analyzed HRV of the R-waves series across the whole sleep/wake period using Kubios HRV Analysis Software 2.2 (Biosignal Analysis and Medical

Imaging Group, University of Kuopio, Finland), according to the Task Force guidelines (Malik et al., 1996). RR peaks were automatically detected by the Kubios software and visually examined by trained technicians. Incorrectly detected R-peaks were manually edited. Missing beats were corrected via cubic spline interpolation. Artifacts were removed using the automatic medium filter provided by the Kubios software. The HRV analysis of the RR series was performed by using an independent lab tool. An autoregressive model (Model order set at 16) (Boardman et al., 2002) was employed to quantify the absolute spectral power (ms^2) in the LF HRV (0.04–0.15 Hz; ms^2) and the HF HRV (0.15–0.40 Hz; ms^2) frequency bands. The LF HRV and HF HRV measures had skewed distributions and as such were transformed by taking the natural logarithm, as suggested by Laborde et al. (2017). From these variables we derived the HF normalized units (HF_{nu}= (HF HRV[ms^2]/ HF HRV[ms^2] + LF HRV[ms^2])*100). Since the LF normalized units are mathematically reciprocal to HF_{nu} (i.e. LF_{nu} =1- HF_{nu}), to avoid redundancy, we computed only the HF_{nu} index, an index often thought to reflect vagal modulation[8]. Besides frequency domain, we also calculated a time domain measure typically used to assess parasympathetic activity, RMSSD. This value is obtained by first calculating each successive time difference between RR intervals in milliseconds. Then, each of the values is squared and the result is averaged before the square root of the total is obtained. Similar to the frequency adjustments, to adjust for the unequal variance in the RMSSD, we report the natural logarithm of RMSSD. Additionally, we included the RR interval as an index of cardiac autonomic control in our analyses.

For the analysis of RR, HR and frequency-domain HRV measures during different sleep stages, consecutive, artifact-free windows of undisturbed sleep were selected across the nap. Each window was 3-min in duration and the 1.5-min preceding and the entire 3-min epoch were free from stage transitions and movement times. Windows were identified and averaged within Stage 2, SWS and REM sleep. We also analyzed 3 min of pre-nap wakefulness (Wake). Epochs of stage 1 and wake after sleep onset were not analyzed, because these periods have not been previously reported

to contribute to memory and are hard to isolate in the recording. This methodology emphasizes consolidated sleep stages and because naps have more fragmented sleep due to increased stage transitions, this method of HRV analysis decreased the number of subjects that could be analyzed.

Data Reduction

104 (Males = 60) young adults were recruited and randomized into three nap conditions (Wake=51, Nap=53). 1 participant were excluded based on Math accuracy (70%). Therefore, for the WM task, we have 103 (Wake=51, Nap=52) participants in our dataset. For ANS measures, 5 participants nap recordings were not collected due to recording computer failures. For Stage 2 sleep, we excluded 6 participants due to no 3-minute window of undisturbed consecutive Stage 2 sleep. For SWS sleep, we excluded 14 participants due to no 3-minute window of undisturbed consecutive SWS. For REM sleep, we excluded 30 participants due to no 3-minute window of undisturbed consecutive REM sleep. In summary, 47 participants were included in Wake; 41 participants were included in Stage 2; 33 participants were included in SWS; 16 participants were included in REM sleep.

Statistical Analyses

In order to investigate within-subject profile of cardiac activity across sleep stages, we used a linear-mixed effect models (LME), which do not depend on limited assumptions about either variance-covariance matrix assumptions (sphericity) or complete data. As the numbers of subjects are different among different sleep stages, LME corrects degrees of freedom with Satterthwaite approximation. Our LME model used a within-subjects factor of stage (Wake, Stage 2, SWS, REM). All comparisons were adjusted by Bonferroni correction. To confirm that there was no difference in WM baseline performance between the two Nap conditions, we used a one-way analysis of variance (ANOVA) with Nap Condition (Wake, Nap) as the between-subject factor, Test 1 as the dependent

variable. To test the difference in WM change across the day, we used a one-way ANOVA with Nap Condition (Wake, Nap) as the between-subject factor, Test 2 – Test 1 as the dependent variable. To examine whether sleepiness level changed with different nap conditions, we used a repeated-measure ANOVA with Nap Condition (Wake, Nap) as the between-subject factor, Session (1 and 2), as the within-subject factor, and KSS as the dependent variable. Pearson correlation coefficients were used to examine the bivariate relationship between HRV variables of interests and WM performance measures, relationship between sleep parameters and WM performance, as well as relationship between KSS and WM performance. To assess the relative importance of HRV variables for WM improvement, we utilized a hierarchical, linear regression approach. In Model 1, baseline WM performance was the independent variable and Test 2 was the dependent variable. In Model 2, we added the HRV factors as independent variables. By comparing Model 1 and 2, we measure the explanatory gain of HRV factors over and above individual differences in WM baseline performance. To compare between two nested models, we conducted a likelihood ratio test. Under the null hypothesis, the full/ restricted model (Model 2) is just as good as the reduced/ unrestricted model (Model 1). Therefore, a significant result on this test indicated that overall model fit is improved after adding the predictors in Model 2.

Results

HRV during Wake and Sleep

Prior studies have reported increasing parasympathetic activity from waking to deeper stages of NREM sleep. In order to test this autonomic profile in each age group, we used an LME model examining HRV variables across sleep stages (Wake, Stage 2, SWS, REM; Table 2.1). We found a stage effect for RR intervals (Figure 2.1a) [$F_{(3,33)} = 15.598$, $p < 0.001$], with a significant lengthening of RR intervals during Stage 2 [$p < 0.001$] and SWS [$p = 0.001$] relative to Wake.

Similarly, RMSSD showed changes across sleep stages (Figure 2.1b p.29) [$F_{(3,33)} = 6.092$, $p = 0.002$], with a significant higher heart rate variability during Stage 2 [$p < 0.001$], and a non-significant difference in SWS [$p = 0.88$] relative to Wake. The HF HRV showed a stage effect (Figure 2.1c) [$F_{(3,33)} = 10.912$, $p < 0.001$], with a higher but not significant vagal tone during Stage 2 [$p = 0.014$] and SWS [$p = 0.74$], relative to Wake. HF_{nu} (Figure 2.1d) showed a stage effect [$F_{(3,33)} = 28.404$, $p < 0.001$], with a marked increase of vagal tone in SWS ($p < 0.001$), compared with Wake. During REM sleep, participants showed significantly shorter RR intervals compared to Stage 2 [$p = 0.001$] and SWS [$p = 0.002$], as well as significantly lower HF_{nu} compared to Stage 2 [$p < 0.001$] and SWS [$p < 0.001$].

Working Memory Performance: Comparing Nap vs Wake Group

Our analysis revealed no significant difference in WM between the two nap conditions at baseline [$F_{(1,101)} = 0.79$, $p = 0.376$]. We compared differences in WM improvement after either a nap or wake period using a one-way ANOVA with Nap condition (Nap vs. Wake) as the independent variables, Test 2-Tset 1 WM performance as the dependent variable. The analysis revealed a main effect of nap condition [$F_{(1,101)} = 3.992$, $p = 0.048$; Figure 2.2], in which participants showed a greater differential benefit from the nap compared to the wake condition.

Repeated-measure revealed no main effect of session or nap condition on sleepiness (KSS), but a significant interaction between session and nap condition [$F_{(1,99)} = 5.445$, $p = 0.021$], where the sleepiness level significantly decreased after the nap. Neither the morning nor the afternoon KSS measures were correlated with WM performances [all ps > 0.23]. Descriptive statistics for KSS were shown in Table 2.2.

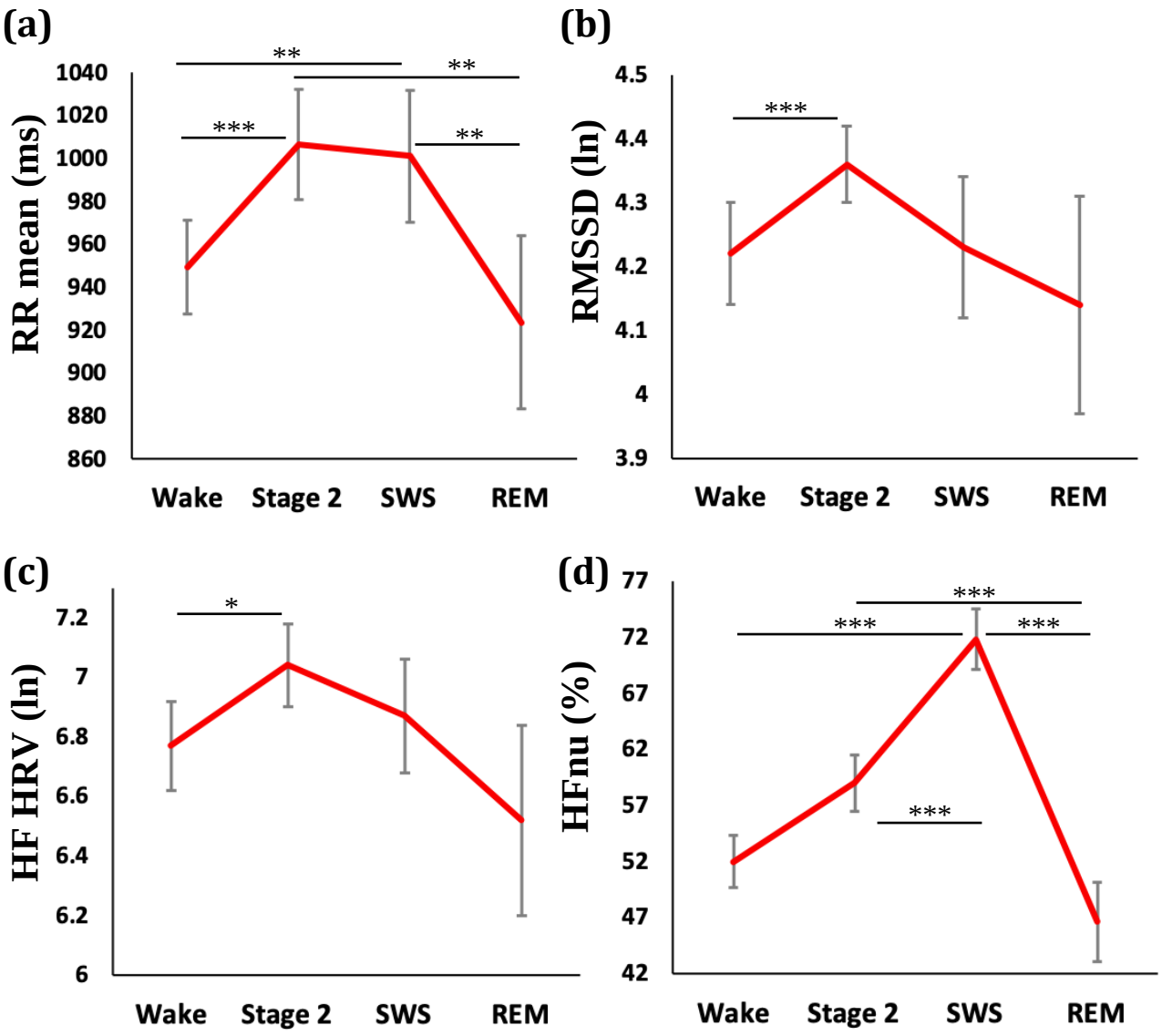


Figure 2.1 HRV profiles during a daytime nap

Heart rate variability (HRV) components across sleep stages. (a) Mean of RR intervals (ms) (b) RMSSD (ln) (c) HF HRV (ln) (d) HRV High-Frequency Power (HFnu). Asterisks above bars indicate significant differences between Sleep stages (*p < 0.05; **p < 0.01; ***p < 0.001). Error bars represent standard error of the mean. The between-stage effects were based on the LME model examining HRV variables across sleep stages (Wake, Stage 2, SWS, REM).

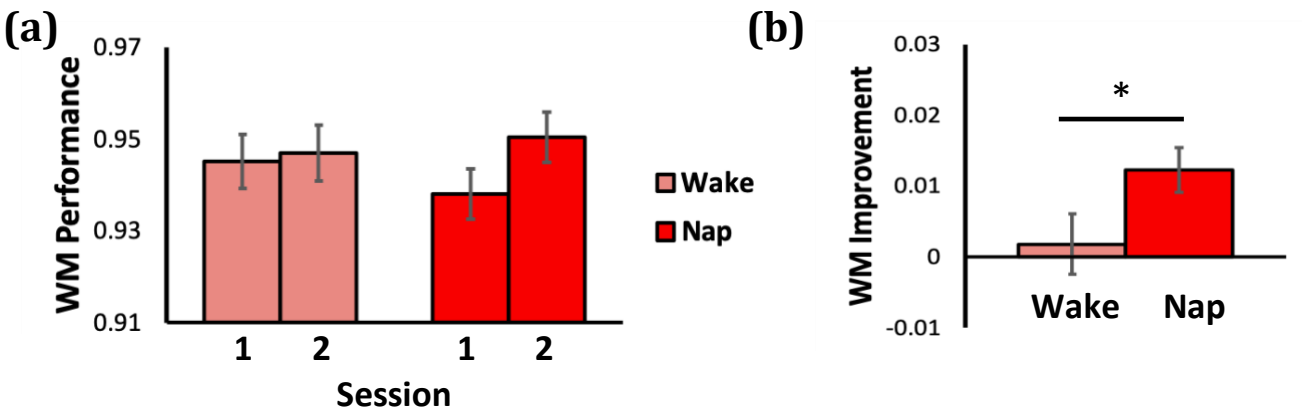


Figure 2.2 WM improves across a daytime nap compared to wake
Working Memory Performance by Nap Condition: (a) Session 1 and 2 performances by Nap Condition: No significant difference in WM between the two nap conditions at baseline (b) WM improvement by Nap Condition: Significant difference in WM improvement after a nap or a period of wake was observed. Asterisks between error bars indicate significant differences between nap conditions (*p < 0.05). Error bars represent standard error of the mean.

Associations between Parasympathetic Activity during Wake and Sleep on Working Memory

Next, we examined the impact of parasympathetic activity during wake and sleep on WM performance and improvement. We used Pearson correlation coefficients to examine the relationship between parasympathetic activity as measured by HF^{nu}, HF HRV (ln), and RMSSD (ln) and WM performance (baseline and improvement). WM baseline performance was not correlated with HRV measures during stage 2 sleep (all ps > 0.150), SWS (all ps > 0.184), REM sleep (all ps > 0.092), or Wake (all ps > 0.439). In alignment with our expectation, WM improvement was positively correlated with SWS HFnu (r = 0.449, p = 0.015, Figure 2.3a p.30). Similar positive, marginally significant associations were also found between WM improvement and HF HRV (ln) as well as RMSSD (ln) during SWS (HF HRV: r = 0.367, p = 0.05, Figure 2.3b; RMSSD: r = 0.347, p = 0.065, Figure 2.3c p.30). However, there was no significant associations between WM improvement and autonomic activities during stage 2 sleep (all ps > 0.434), REM sleep (all ps > 0.180), or Wake

(all ps > 0.584). Furthermore, sleep alone (total time in bed, total sleep time and time in each stage (minutes)) was not significantly correlated with WM baseline or improvement (all ps > 0.41).

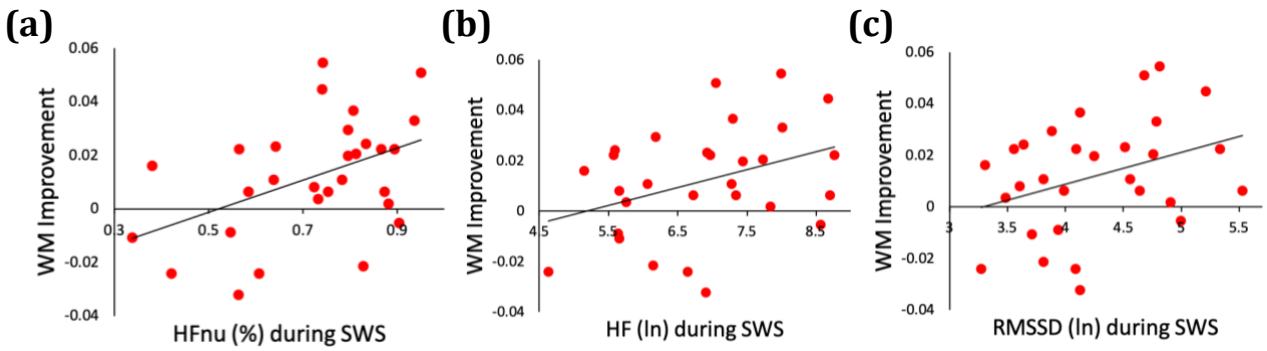


Figure 2.3 WM improvement correlated with HRV during SWS
Working Memory improvement and Autonomic Activity. Association between WM improvement and (a) HFnu (r = 0.449, p = 0.0145) (b) HF HRV (ln) during SWS (r = 0.367, p = 0.05); (c) RMSSD (ln) during SWS (r = 0.347, p = 0.065).

Next, we assessed the importance for memory performance of ANS activity using hierarchical, linear regressions. Two linear regression models were built to predict WM session 2 performance. In Model 1, baseline WM performance was the independent variable. In Model 2, we added HFnu during SWS. Model 1 was significant ($F_{(1,27)}$= 70.26, p< .001; adj R^2 = .712), suggesting that individual difference at baseline has a strong impact on session 2 performance. Model 2 also significantly predicted performance ($F_{(2,26)}$= 42.71, p< .001; adj R^2 = .749) with HFnu as a significant predictor (p= .035). Comparing Model 1 and 2 using a likelihood ratio test, we found that Model 2 was a better fit compared to Model 1 (p= .025). In summary, while baseline WM performance provides large amount of shared variance with session 2 WM performance, HFnu during SWS added significantly more explained variation on WM performance.

Discussion

Our health is maintained through variability that allows our biological system to adjust its resources to match specific situational demands. Heart rate variability (HRV) reflects an individual's ability to adapt the autonomic nervous system to moment-to-moment changes in her environment (Thayer & Lane, 2009b). HRV has been associated with both cognitive and health outcomes, as well as linked to age-related decreases in physiological functioning. Although sleep has been shown to modulate HRV (Baharav et al., 1995; Cellini et al., 2016; Trinder et al., 2001; Whitehurst et al., 2018), the impact of this modulation has not been examined in the context of sleep related WM gains. In the current study, we investigated the functional consequence for WM of fluctuations in autonomic activity during a daytime nap in healthy young adults. We replicated the previously reported increase in parasympathetic activity in NREM sleep during daytime naps (Cellini et al., 2016). Additionally, participants showed a sleep-dependent boost in WM after sleep, and HRV during sleep was associated with WM improvement. In summary, our results provide evidence of an important role of parasympathetic activity during sleep in WM improvement in healthy young adults.

Nap HRV

Similar to previous nap (Cellini et al., 2016) and nighttime sleep studies (Whitehurst et al., 2018), we found vagally-mediated parasympathetic activity increased from waking to NREM sleep. These changes suggest a shift of the ANS from sympathetic to parasympathetic regulation in the transition from wakefulness to sleep. Given the parasympathetic dominance during sleep compared with wake, nighttime sleep has been described as a "cardiovascular holiday" (Trinder et al., 2012). Overall autonomic balance between parasympathetic and sympathetic branches is beneficial for health and cognition, whereas autonomic imbalance, indexed by low HRV and elevated sympathetic activity is associated with increased morbidity and various pathological conditions, such as

cardiovascular disease, diabetes, and Alzheimer's disease. Moreover, increased parasympathetic activity has been shown to reduce proinflammatory cytokines, and sympathetic hyperactivity is associated with increased proinflammatory cytokine production (Jarczok et al., 2015). With older adults, parasympathetic activity is less modulated during sleep compared with young adults, and no significant sleep-stage dependent variations are reported (Brandenberger et al., 2003). This profile reveals a tendency for increased sympathetic arousal and a predominant loss of parasympathetic activity in aging, which may be related to the increased number of awakenings during sleep and lower duration of SWS in this age group. The current findings in young adults of parasympathetic enhancement during sleep, and its role in WM improvement have implications for potential translational treatment strategies that target parasympathetic activity during sleep, and also suggest future studies examining the impact of age-related changes in ANS profiles on cognition.

Nap and Working Memory: The Functional Roles of Cardiac Activities

While a large body of studies has demonstrated the negative impact of sleep loss preceding WM performance (Choo et al., 2005; Goel et al., 2009; Pasula et al., 2018), studies into the effect of post-training sleep on WM improvement are few, and none have examined this question in the context of ANS activity. We show that, compared with wake, WM improves after a daytime nap, similar to prior studies using a nap (Lau et al., 2015b) and nocturnal sleep (Kuriyama et al., 2008b; Zinke et al., 2018b), suggesting that sleep might provide an optimal brain state that facilitate WM training. We did not, however, find a significant correlation between waking HRV (as assessed with RMSSD, HF HRV, and HFnu) and WM in our sample. Although prior reports of HRV and WM have reported that people with higher vagally-mediated HRV perform better on WM tasks, these results were based upon median splits of the data on HRV or WM performance (Giuliano et al., 2017; Hansen et al., 2003; Laborde et al., 2015; Spangler & Friedman, 2017). Direct correlations between waking HF HRV and WM yielded mixed results, with one study reporting a moderate correlation

(Laborde et al., 2015), another yielding a borderline correlation (Hansen et al., 2003), and one showing no significant relation (Giuliano et al., 2017). In the current study, we did not find significant correlations between waking HRV and WM baseline performance or WM improvement, but instead showed a consistent pattern of an association between HRV during SWS and WM, where greater parasympathetic activity was associated with better WM improvement. Given these results, SWS, a period of naturally high levels of parasympathetic tone, should also be considered as a viable outcome measure of cardiac autonomic activity. Furthermore, parasympathetic activity during SWS, a potential biomarker of successful WM training, needs to be further studied to understand the neurophysiological mechanisms of sleep-related WM gains.

Working Memory Model: Slow Wave Sleep, Parasympathetic Activity and Prefrontal Functioning

We propose a conceptual model (Figure 2.4), that illustrates the interaction between sleep, autonomic activity, and prefrontal brain function that together and independently contribute to WM processing. We build this model on the following corpus of findings. First, studies in healthy young adults have established that people with higher waking HRV show better executive function (including WM), which is a set of cognitive abilities strongly supported by the prefrontal cortex (Thayer et al., 2009). This brain region is implicated in top-down control of the vagus nerve (Shaffer et al., 2014), and prefrontal cortical thickness is positively associated with vagally-mediated HRV during wake in both young and older adults (Yoo et al., 2018). Additionally, SWS and vagal activity are highly associated in both young and older adults (Brandenberger et al., 2003). Furthermore, the current study demonstrated the importance of sleep HRV for WM in healthy young adults. Taken together, prefrontal brain functioning, SWS, and parasympathetic activity, might together support sleep-related WM improvement. Aging is characterized by a decline in executive functions (Kirova et al., 2015), prefrontal brain atrophy (Mander et al., 2013; Salat et al., 2004), impaired sleep (Mander et al., 2017), as well as decreased vagal tone (O'Brien et al., 1986). Though studies have

established that aging is accompanied by a decline in vagally-mediated HRV during wake (De Meersman & Stein, 2007), little is known about age-related changes in HRV during sleep. Thus, it is unclear how the impact of aging on: 1) prefrontal function, 2) sleep, and 3) parasympathetic activity may be potential mediators of WM training. It remains to be seen whether the loss of parasympathetic activity during NREM sleep in older adults may mediate decreases in executive function, and/or recruitment of different brain areas to compensate for prefrontal loss. Future studies comparing younger and older populations with simultaneous brain imaging, EEG and ECG during WM training and sleep will be the next steps to further elucidate this complex interaction.

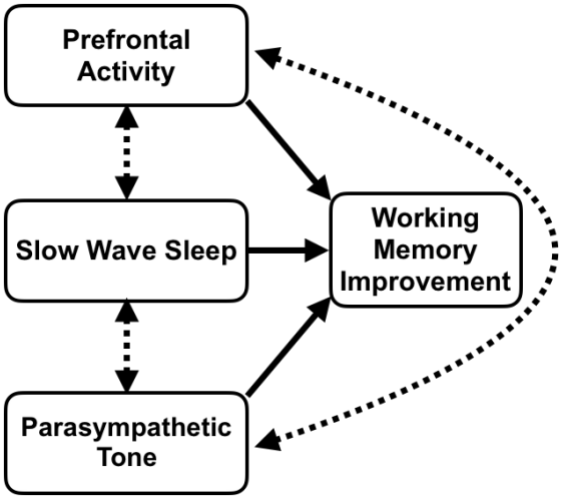


Figure 2.4 Conceptual Model
We illustrate the interaction between three biological markers, Prefrontal Brain Activity, Slow Wave Sleep, and Parasympathetic Tone, which together and/or independently lead to working memory improvement in young adults.

Limitations

The current study has several limitations that need to be addressed. First, one limitation of this study is the reduction in subject numbers due to HRV methodological constraints. Specifically, standard practice for HRV analyses (Malik et al., 1996) requires assessment of HRV over a five-minute period of a consistent sleep stage. Due to the large amount of sleep transitions present in a daytime nap, this method decreased the number of available subjects and may have biased the sample towards less fragmented sleepers. In order to retain more statistical power, future studies should confirm these results in HRV assessments during nocturnal sleep. On the same topic, this

limitation in data may underpower certain statistical comparisons, in particular for nap designs that have limited sleep compared with full night designs. For example, the current results found a significant association between performance and HFnu only, whereas the other markers of parasympathetic activity, though in a similar positive direction, did not reach statistical significance. This discrepancy may have been due to low power within certain sleep stages, and should be further investigated in a nighttime sleep study, which provides longer bouts of deep sleep.

Conclusion

The present study investigated the role of sleep HRV during a daytime nap in WM performance across a day. Our results confirmed that sleep benefited WM. Moreover, we showed the first evidence that the autonomic activity during sleep, but not wake, played a crucial role in WM. Thus, for heathy young adults, a daytime nap can serve as a "mini cardiovascular break" that benefits executive functions.

Chapter Three: The role of autonomic-central couplings during sleep on working memory improvement

Abstract

Working memory (WM) is an executive function that can improve with training. However, the precise mechanism for this improvement is not known. Studies have shown greater WM gains after a period of sleep than a similar period of wake, and correlations between WM improvement and slow wave activity (SWA; 0.5–1 Hz) during slow wave sleep (SWS). A different body of literature has suggested an important role for autonomic activity during wake for WM. A recent study from our group reported that the temporal coupling of Autonomic/Central Events (ACEs)during sleep was associated with memory consolidation. We found that heart rate bursts (HR bursts) during non-rapid eye movement (NREM) sleep are accompanied by increases in SWA and sigma (12–15 Hz) power, as well as increases in the high-frequency (HF) component of the RR interval, reflecting vagal rebound. In addition, ACEs predict long-term, episodic memory improvement. Building on these previous results, we examined whether ACEs also contribute to gains in WM. We tested 104 young adults in an operation span task (OSPAN) in the morning and evening, with either a nap (n = 53; with electroencephalography (EEG) and electrocardiography (ECG)) or wake (n = 51) between testing sessions. We identified HR bursts in the ECG and replicated the increases in SWA and sigma prior to peak of the HR burst, as well as vagal rebound after the peak. Furthermore, we showed sleep-dependent WM improvement, which was predicted by ACE activity. Using regression analyses, we discovered that significantly more variance in WM improvement could be explained with ACE variables than with overall sleep activity not time-locked with ECG. These results provide the first evidence that coordinated autonomic and central

events play a significant role in sleep-related WM improvement and implicate the potential of autonomic interventions during sleep for cognitive enhancement.

Introduction

Working memory (WM), the ability to retain, manipulate, and update information over short periods of time, is essential to higher order cognition (e.g. language comprehension, reasoning, and general intelligence; Engle and Kane 2004) and for performing many daily activities (Cantarella et al., 2017; Kane et al., 2007). WM is prone to age-related cognitive decline, which is evident in midlife, and becomes particularly pronounced in older age (age > 75) (Hale et al., 2011). Considering the importance of WM for cognitive functions and the detrimental effects of age-related WM declines, the possibility of improving WM performance to facilitate cognitive health has been advanced (Soveri et al., 2017; Zinke et al., 2013). Importantly, recent studies suggest that WM capacity is subject to experience-dependent change (Au et al., 2015; Jaeggi et al., 2008; Karbach & Verhaeghen, 2014), but the mechanism underlying this change is not understood. Recent studies suggest a role for sleep (Ferrarelli et al., 2019; Pugin et al., 2015; Sattari et al., 2019). The purpose of the current study is to identify sleep-specific features that support WM enhancement.

Sleep plays an important role in the maintenance and improvement of a wide range of cognitive processes (Lowe et al., 2017; Mednick et al., 2011; Rasch & Born, 2013; Whitney et al., 2017), including executive functions, (e.g., sustained attention and WM (Könen, Dirk, & Schmiedek, 2015; Vriend et al., 2013; Cellini et al. 2015; Goel et al. 2009; Lo et al. 2012)). Sleep deprivation negatively impacts WM performance as measured with digit span (Quigley, Green, Morgan, Idzikowski, & King, 2000) and the N-back task (Choo, Lee, Venkatraman, Sheu, & Chee, 2005). Additionally, studies suggest that sleep between WM training sessions, compared to wake, may be critical for enhancing WM performance (Zinke et al., 2018b; Kuriyama et al., 2008b; Lau et al., 2015b; Chen, Whitehurst, & Mednick, 2020). For example, training participants on an n-back task

over several sessions improved accuracy of performance, but only if the interval between training sessions contained nocturnal sleep (Zinke et al., 2018b; Kuriyama et al., 2008b) or a nap (Lau et al., 2015b), but not wake. Recent observations suggest that SWS may provide an optimal brain state for modification of prefrontal functioning. SWS constitutes between 10 and 25% of total sleep time (Ohayon et al., 2004) and is thought to play an important role in cerebral restoration and recovery (Horne, 1992), and SWA is a global index of sleep homeostasis (Borbély & Achermann, 2000). Several studies have shown a specific association between EEG activity during SWS in the enhancement of WM suggesting that SWA may reflect localized, experience-dependent, cortical plasticity (Huber et al., 2004; Miyamoto et al., 2017; Rodriguez et al., 2016). Specifically, Pugin and colleagues demonstrated fronto-parietal increases in SWA following WM training, and the magnitude of SWA correlated with WM performance after three weeks of training (Pugin et al., 2015). Furthermore, SWA predicted WM gains across a period of sleep in both young (Ferrarelli et al., 2019) and older adults (Sattari et al., 2019). Taken together, these studies suggest that experience-induced changes in SWA support efficient WM improvement.

In recent years, a number of studies have explored the association between central and autonomic activity during sleep, offering promising new perspectives to understand brain-body interplay in humans (Ako et al., 2003; Brandenberger et al., 2001b; Thomas et al., 2014; Whitehurst et al., 2020). For example, a recent study investigated the relationship between cardiac activity and K-complexes (KC; 0.5-1 Hz)-a positive-negative-positive waveform during Stage 2 sleep similar to slow oscillations-and demonstrated that KCs were associated with a biphasic cardiac response, with a marked heart rate acceleration followed by a gradual deceleration (de Zambotti et al., 2016). Interestingly, this biphasic fluctuation in heart rate has also been shown to coincide with bursts of K-complexes and delta waves (Sforza et al., 2000), which, together, indicate a synchronization of central and autonomic events. Furthermore, our group recently identified cardiovascular events during NREM sleep, termed heart rate bursts, that last 2-3 seconds and occur mostly in Stage 2 and

SWS (Naji et al., 2019). Heart rate bursts are temporally coincident with EEG activity, including SWA and spindle/sigma activity (12-15Hz) and are followed by vagal rebound reflected in a surge in the high frequency component (HF; 0.15–0.4 Hz) of the ECG. The increased SWA and Sigma activity before the HR bursts and the vagal activity after the HR burst were termed as ACE activity (ACE SWA, ACE Sigma, and ACE RRHF, respectively). These Autonomic/Central Events (ACEs) significantly predicted the magnitude of long-term, episodic memory improvement to a greater extent than non-ACE sleep activity and overall sleep activity. The current study builds on these findings by investigating the role of ACE activity in WM improvement.

We tested whether ACE activity during SWS sleep supports sleep-related improvement in the Operation Span Task (OSpan), a dual-task consisting of a processing subtask and a short-term memory subtask that has been commonly used to test central constructs of WM. In summary, the current study aimed: (1) to replicate ACE activity in sleep during a daytime nap; and (2) to determine the impact of ACE activity during SWS on WM gains. Given prior associations between SWA and WM improvement, we hypothesized that ACE SWA would be significantly associated with WM gains across the nap. We considered ACE sigma activity as a positive control that would not be correlated with WM improvement.

Methods

Participants

104 young (Age:17-23 [Mean=20.7, SD= 2.95], 64 males) healthy adults with no personal history of neurological, psychological, or other chronic illness provided informed consent, which was approved by the University of California, Riverside Human Research Review Board. Participants were randomized to either have a 2-hour nap opportunity monitored with polysomnography (PSG) (n=53), stay awake (n=51), where subjects engaged typical daily activities with actigraph monitoring. Participants included in the study had a regular sleep-wake schedule

(reporting a habitual time in bed of about 7–9 h), and no presence or history of sleep, psychiatric, cardiovascular, or neurological disorder determined during an in-person, online, or telephone interview. Participants received monetary compensation for participating in the study. For PSG measures, 4 participants' nap recordings were not collected due to recording computer failures. Among the 50 participants whose PSG were recorded, 2 of them did not have stage 2 sleep and 13 of them did not have SWS.

Working memory task

The current study used the Operation Span Task (OSpan; Turner & Engle, 1989) as a measure of WM performance, which requires participants to solve a series of math operations while trying to memorize a set of unrelated letters. The task was programmed in Matlab (The MathWorks Inc., 2015) using Psychtoolbox (Kleiner et al., 2007). The task included 3 practice and 20 test trials. Participants were tested in letter strings of seven. For each letter string, participants were shown a series of math problems that they had to confirm were correct within 3 seconds, using pre-determined responses on the keyboard. After each equation, a letter would appear on the screen and the subject was instructed to remember each letter. At the end of each string, the participant was instructed to recall the letters in the order presented by typing responses on a computer keyboard. Immediately after each trial, the next letter string would be presented. If the participants forgot one of the letters in a trial, they were instructed to provide their best guess. In addition, to decrease trade-off between solving the operations and remembering the letters, a 70% accuracy criterion on the math operations was required for all the participants. We excluded 6 participants based on this criterion. We calculated performance as: number of correct letters recalled in the correct order/ total number of letters in the string. For assessing change in performance from session 1 and session 2, we calculated the difference in performance between the two sessions (session 2 – session 1).

Study Procedure

Participants were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. Participants filled out sleep diaries for one week prior to the experiment and wore wrist-based activity monitors the night before the study (Actiwatch Spectrum, Philips Respironics, Bend, OR, USA) to ensure participants were well-rested, defined as at least 7 hours on average during the week and the eve of the experimental day. On the experimental day, participants arrived at the Sleep and Cognition lab at 10:00AM and had EEG electrodes attached, followed by an Operation Span (OSpan) working memory task. Nap/Wake interventions occurred between 1:30-3:30 PM. At 1:30PM, subjects in the Nap group were given 2-hours time-in-bed to obtain up to 90-min total sleep time during which their sleep were polysomnographically-recorded. Sleep was monitored online by a trained sleep technician. Subjects in the Wake group were asked not to nap, exercise, or consume caffeine or alcohol, and were monitored with actigraphy during the active wake period. All subjects were retested on the memory task between 4 and 4:30PM. Subjects completed the Karolinska Sleepiness Scale (KSS, Åkerstedt et al., 1990) questionnaire two times throughout the experimental day; at the start of each WM task (Session 1 and Session 2) to report their sleepiness. KSS is a 9-point Likert scale often used when conducting studies involving self-reported, subjective assessment of an individual's level of drowsiness at the time, in which a higher score yields a sleepier state.

Sleep recording and scoring

Polysomnography (PSG) data, including electroencephalogram (EEG), electrocardiogram (ECG), chin electromyogram (EMG), and electrooculogram (EOG), were collected using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10–20 System (Jasper, 1958). Electrodes included 24 scalp, two electrocardiogram (ECG), two electromyogram (EMG), two electrooculogram (EOG), 1 ground, and 1 on-line common reference

channel. EEG signals were recorded at a 1000 Hz sampling rate and referenced on-line to the common reference channel. Scalp EEG and electrooculographic (EOG) electrodes were referenced to unlinked contralateral mastoids (F3/A2, F4/A1, C3/A2, C4/A1, P3/A2, P4/A1, O1/A2, O2/A1, LOC/A2, ROC/A1), and two EMG electrodes were attached under the chin and referenced to each other. After recording, all data were then digitized at 256 Hz. High-pass filters were set at 0.3 Hz, and low-pass filters were set at 35 Hz for EEG and EOG electrodes. A notch filter was set at 60 Hz. The EEG data were scored using Hume, a custom MATLAB toolbox. The records were scored in 30-second epochs using eight scalp electrodes: Frontal (F3, F4), Central (C3, C4), Parietal (P3, P4), and Occipital (O1, O2). Next, all epochs of the filtered data with artifacts and arousals were identified by visual inspection and rejected. Five sleep stages (i.e., wake, Stage 1, Stage 2, SWS, and REM) were reclassified in continuative and undisturbed 3-min bins and the bins were used for further analysis. Descriptive statistics for sleep architecture were shown in Table 3.1.

Power spectral analysis

The EEG power spectrum was computed using the Welch method (4 sec Hanning windows with 50 % overlap). The frequency for sigma power was 12- 15Hz and for SWA was .5–1 Hz. For RR time-series, the power spectral estimation was performed by the autoregressive model and the model order was set at 16. Summary statistics for EEG power spectrum were shown in Table 3.2.

Heart-beat detection

We analyzed HRV of the R-waves series using Kubios HRV Analysis Software 2.2 (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland), according to the Task Force guidelines (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). RR peaks were automatically detected by the Kubios software and visually examined by trained technicians. Incorrectly detected R-peaks were manually edited. Next, the data was passed to a MATLAB (MathWorks) based algorithm to measure perform further analyses.

Electrocardiogram (ECG) data were acquired at a 1000-Hz sampling rate using a modified Lead II Einthoven configuration. The ECG signals were filtered with a passband of 0.5-100 Hz by Butterworth filter. R waves were identified in the ECG using the Pan-Tompkins method. In order to extract continuous RR tachograms, the RR intervals were resampled (at 4 Hz for power spectrum estimation) and interpolated by piecewise cubic spline. Zero-phase Butterworth filters were applied to the interpolated RR time-series to extract RR_{HF}.

HR burst detection

Within 3-min bins of the RR time-series during wake and sleep stages, the HR burst events were detected as RR intervals shorter than two standard deviations below the mean. Summary for HR bursts Density were shown in Table 3.3.

Time-locked analysis

In order to calculate changes in SWA and sigma power around the HR burst, the Hilbert transform was applied on filtered EEG signals in bands of interest (0.5–1 Hz for SWA and 12–15 Hz for sigma activity). To assess the HF amplitude fluctuation around the HR burst (RR_{HF}), the Hilbert transform was applied on RR_{HF} (0.15–0.4 Hz). See Naji et al 2019 for detailed methods.

ACE Change scores

We investigated ACE coupling during wake and sleep stages by tracking fluctuations in the EEG in a 20-sec window from 10 second before to 10 second after the HR burst peak. As we were specifically interested in sleep EEG activity previously demonstrated to correlate with WM improvement, we focused on SWA as our primary frequency band of interest and sigma activity as a positive control band. In addition, we examined RR_{HF} in the ECG channel, about which we did not have a specific hypothesis.

EEG/ECG data were binned into 5-sec intervals within the 20-sec windows around the HR burst, named -10, -5, +5, +10 window. The average RR_{HF}, SWA, and sigma activity were calculated in each of the four 5-sec windows. For non-ACE brain activity, we calculate average RR_{HF}, SWA, and sigma activity in periods with no HR burst (including 20 s windows around them). We computed ACE change scores for each 5-sec interval as follows: (ACE activity in each 5 s interval – non-ACE activity)/ (ACE activity in each 5 s interval + non-ACE activity). We computed similar change scores for RR_{HF}. Change scores in frontal areas were averaged across F3 and F4 channels and activity in central areas were averaged across C3 and C4. Besides ACE and non-ACE activity, overall sleep values (SWA and sigma power) were calculated as average EEG power in the entire sleep stage (regardless of ACE or non-ACE). Given prior findings, we specifically focused two ACE change scores when examining the role of ACE on cognition: (1) PreBase: the change score of the -5 window, and (2) PrePost: ACE activity in the -5 window subtracted from +5 window. Summary for ACE change scores during SWS and Stage 2 were shown in Table 3.4a and 3.4b, respectively. Figure 3.1 showed an example of ACE time-locked analysis.

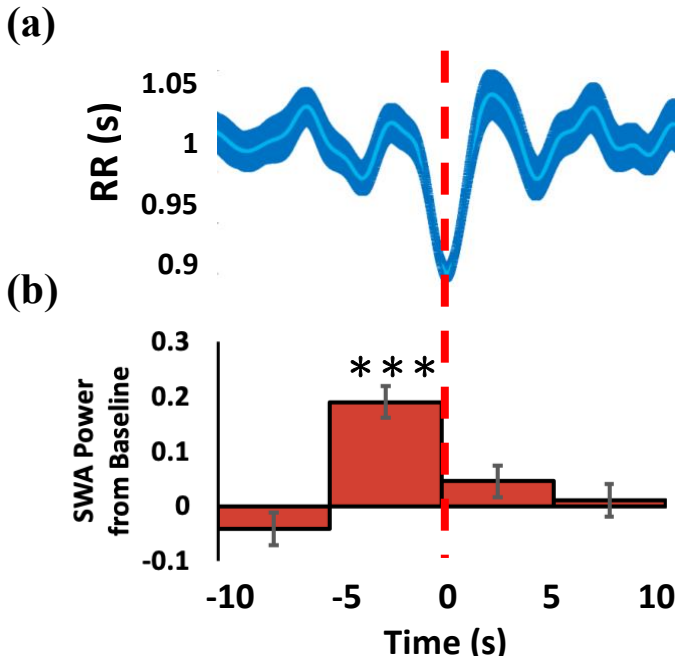


Figure 3.1 Autonomic-central events (ACEs) coupling analysis
Heart-rate-bursts and SWA change scores time-locked on HR bursts during SWS.
(a) Average of the HR bursts (b) ACE SWA change scores show a significant increase in the -5 window.
Asterisks indicate significant differences between a change score in a bin and zero (non-ACE baseline) after Bonferroni correction for multiple comparisons (***p<.001).

Data Reductions

104 (Males = 64) young adults were recruited and randomized into the Wake condition = 51 or the Nap condition = 53. 3 participants in the Nap condition and 1 participant in the Wake condition were excluded based on math accuracy (70%) during Session 1. 1 participant in the Nap condition was excluded based on math accuracy (70%) during Session 2. Therefore, for the WM task, we have Wake condition =50 and Nap condition =49 participants in our dataset. For sleep data, 2 participants nap recordings were not collected due to recording computer failures, so there were 51 subjects included in the sleep analyses. Among the 51 subjects, we were unable to detect stable 3-min bins of Stage 2 sleep for 2 of them, so there were 49 subjects included in the Stage 2 data. Among the 49 subjects, we were unable to detect stable 3-min bins of SWS for 11 of them, so there were 38 subjects included in the SWS data. Hence, we have 32 subjects for correlation and regression as there were 32 subjects who had both WM data and 3-min bins of SWS.

EEG Fluctuation Around the HR Bursts

In order to investigate within-subject profiles of ACE activity across sleep stages, channels, and windows, we used a linear-mixed effect models (LME), which do not depend on limited assumptions about variance-covariance matrix assumptions (sphericity). Additionally, LME models eliminate the need of averaging epochs across sleep stages and allow inclusion of an unbalanced number of observations per subject in the analyses. Moreover, LME models take into account the influence of factors whose levels are extracted randomly from a population (i.e. participants), thus yielding more generalizable results (Baayen et al., 2008).

We built a separate model for each change score (ACE SWA, ACE Sigma, and ACE RR_{HF}), using participant as crossed random effects and Stage (Stage 2, SWS), Channel (Frontal, Central), and Window (-10, -5, +5, +10) as within-subject fixed effects. Post hoc comparisons were corrected using the Bonferroni method.

Furthermore, a one-sample t-test for each change score compared to zero was performed to capture if the modulation around the HR bursts were significant. Bonferroni corrections were used to adjust multiple testing (total 40 t-tests). Asterisks in Table 3.5a and 3.5b significant differences between a change score in a bin and zero (non-ACE baseline).

Correlations

To investigate the contribution of ACE vs non-ACE events to WM improvement across the nap, we computed Pearson's correlations with WM improvement. We ran total 26 correlations. Multiple testing was corrected using Benjamini–Hochberg procedure with critical value for a false discovery rate of 0.1. The adjusted critical values (α) were added next to each significant correlation report.

Regression Models

To assess the relative importance of ACE and non-ACE activity for WM improvement, we utilized a hierarchical, linear regression approach. Two linear regression models were built to predict WM gain. In Model 1, Session1 WM performance and overall frontal SWA in SWS were the independent variables. In Model 2, we added the ACE change scores (PreBase & PrePost) for frontal SWA in SWS. Baseline WM performance was included in the models as a covariate to account for individual differences in WM capacity (Matysiak et al., 2019). The regression results for the averaged frontal and central activity are tabulated in Table 3.6a and Table 3.6b, respectively. By comparing Model 1 and 2, we measure the explanatory gain of ACE values over and above general sleep EEG and WM capacity for WM improvement.

Results

Working Memory Performance: Comparing Nap vs Wake

Our analysis revealed no significant difference in WM between the two nap conditions in Session 1 [$F_{(1,101)} = 0.804$, $p = 0.372$; Figure 3.2a]. We compared differences in WM improvement after either a nap or wake period using a one-way ANOVA with Nap condition (Nap vs. Wake) as the independent variables, WM improvement as the dependent variable. The analysis revealed a main effect of nap condition [$F_{(1,101)} = 5.734$, $p = 0.0185$; Figure 3.2b], in which participants showed a greater differential benefit from the nap compared to the wake condition.

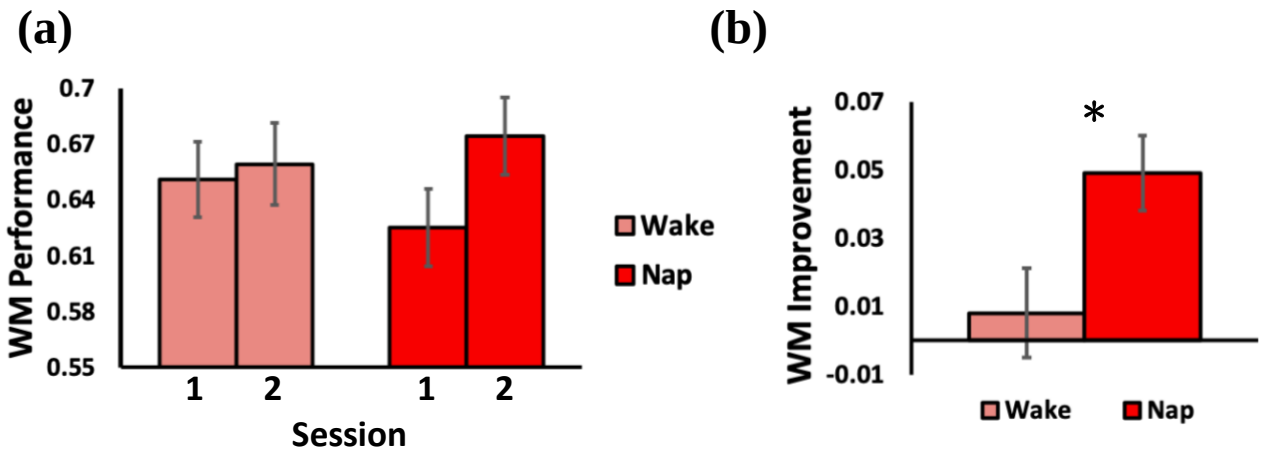


Figure 3.2 WM improves across a nap

Working Memory Performance by Nap Condition:
(a) Session 1 and 2 performances by Nap Condition
(b) WM improvement by Nap Condition: Significant difference in WM improvement after a nap or a period of wake was observed.
Asterisks between error bars indicate significant differences between nap conditions (*p < 0.05). Error bars represent standard error of the mean.

EEG power is modulated by RR phase

For SWA change scores [Figure 3.3a, 3.3b], we found a significant main effect of windows ($F_{(3,632)}$ = 129.518, p< .0001), a main effect of sleep stages ($F_{(1,632)}$ = 5.861, p=.0158) and an interaction between windows and sleep stages ($F_{(3,632)}$ = 13.013, p< .0001). Post hoc comparisons revealed that SWA change scores during the -5 window (prior to the HR burst) were greater than the rest three windows during Stage 2 (all ps < 0.0001), as well as during SWS (all ps < 0.0001), adjusted by Bonferroni correction. No main effect or interaction effect of channels were found. SWA change scores during the -5, +5, and +10 window were greater during SWS, compared to Stage 2.

For Sigma change scores [Figure 3.3c, 3.3d], we found a significant main effect of windows ($F_{(3,632)}$ = 91.537, p< .0001), and an interaction between windows and sleep stages ($F_{(3,632)}$ = 15.268, p< .0001). Post hoc comparisons revealed that Sigma change scores during the -5 window (prior to the HR burst) were greater than the rest three windows during Stage 2 (all ps < 0.0001), as well as during SWS (all ps < 0.0001), adjusted by Bonferroni correction. Furthermore, the +10 window during Stage 2 showed significantly lower change scores than the +5 window (ps < 0.001). No main effect or interaction effect of channels were found. Sigma change scores during the -5 and +10 window were greater and lower during Stage 2, compared to SWS, respectively.

For RR_{HF} change scores [Figure 3.3e], we found a significant main effect of windows ($F_{(3,292)}$ = 37.223, p< .0001). Post hoc comparisons revealed that RR_{HF} change scores during the +5 window (prior to the HR burst) were greater than the rest three windows during Stage 2 (all ps < 0.0001), as well as during SWS (all ps < 0.0466), adjusted by Bonferroni correction. Furthermore, the -5 window during Stage 2 showed significantly greater change scores than the -10 and +10 window during Stage 2 (ps < 0.032). No main effect or interaction effect of sleep stages were found.

Lastly, our t-test showed significant differences between SWA/ Sigma change scores during the -5 window (prior to the HR burst) and zeros. In addition, there were significant differences between RR_{HF} change scores during the -5 and+5 window and zeros, adjusted by Bonferroni correction. Asterisks in Table 3.5a-b significant differences between a change score in each bin and zero (non-ACE baseline).

Taken together, we replicated the profile of ACE activity in Naji et al., with sigma and SWA power in Stage 2 and SWS increased from overall average to a maximum level prior to the peak of the HR bursts (-5 window), and returned to average post-HR-peak, and RR_{HF} increased from average and reached the maximum level after the peak of the HR bursts (+5 window).

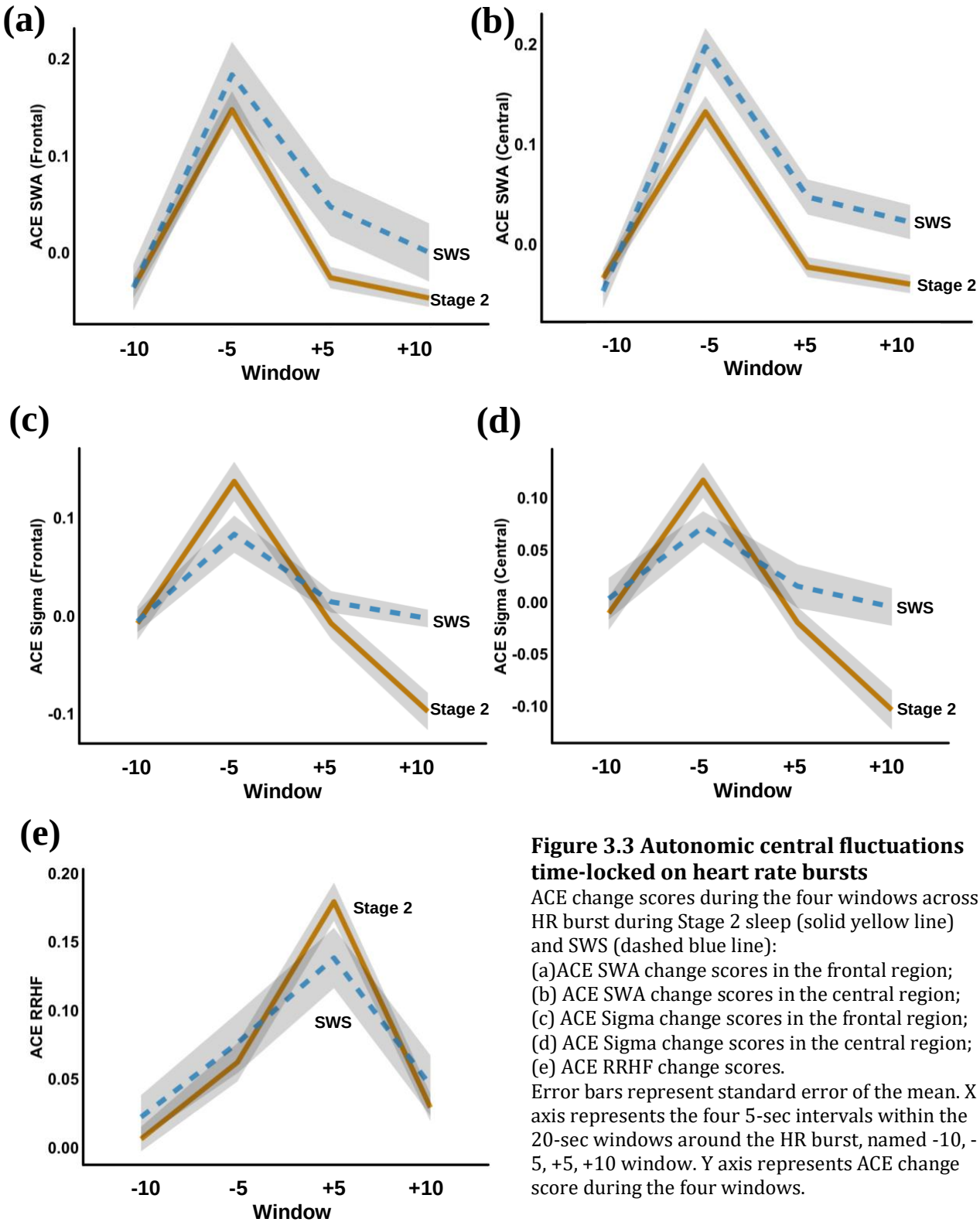


Figure 3.3 Autonomic central fluctuations time-locked on heart rate bursts

ACE change scores during the four windows across HR burst during Stage 2 sleep (solid yellow line) and SWS (dashed blue line):
(a)ACE SWA change scores in the frontal region;
(b) ACE SWA change scores in the central region;
(c) ACE Sigma change scores in the frontal region;
(d) ACE Sigma change scores in the central region;
(e) ACE RRHF change scores.
Error bars represent standard error of the mean. X axis represents the four 5-sec intervals within the 20-sec windows around the HR burst, named -10, -5, +5, +10 window. Y axis represents ACE change score during the four windows.

Correlations with WM Improvement

As predicted, WM improvement was positively correlated with ACE SWA change scores in PreBase (Figure 3.4a p.52 Frontal: r= .447, p= .012, α=.0154; Figure 3.4c p.52 Central: r= .524, p= .003, α= .0077, as well as PrePost (Figure 3.4b p.52 Frontal: r= .560, p= .001, α= .0038; Figure 3.4d p.52 Central: r= .455, p= .010, α=.0115) during SWS. Interestingly, the correlations between WM improvement and overall SWA power in SWS were not significant (see Figure 3.5; all ps > .668).

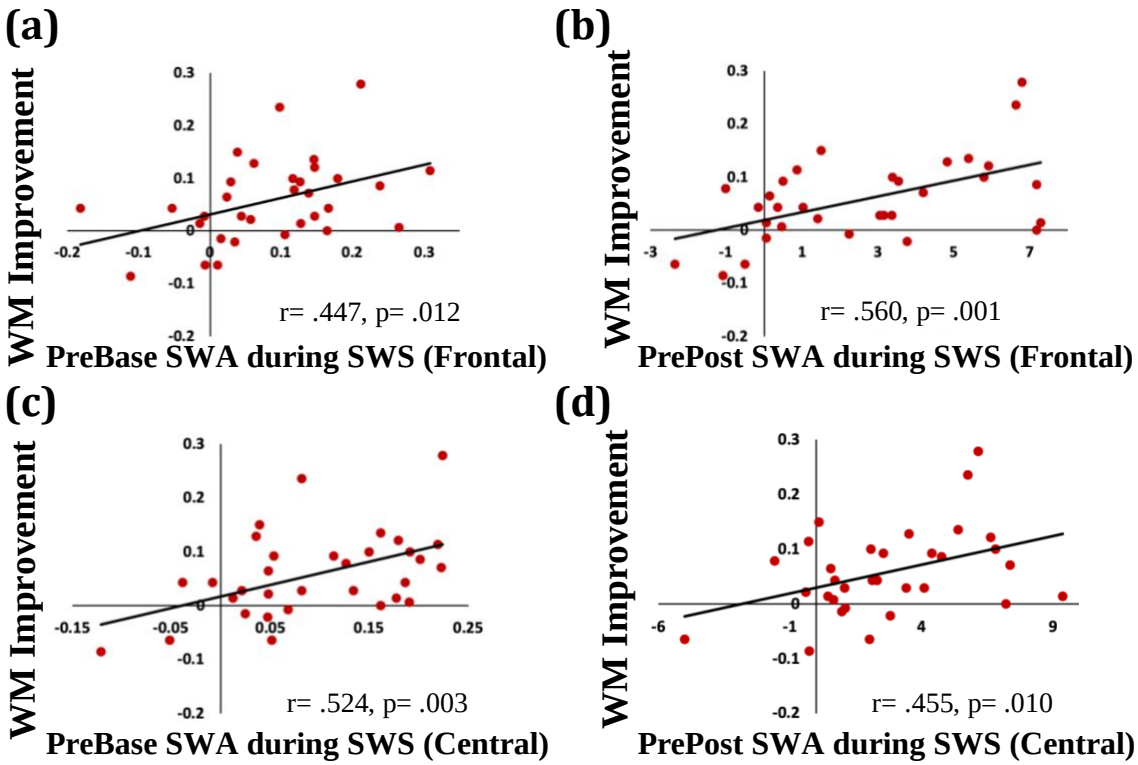


Figure 3.4 WM improvement correlated with autonomic-central events

Correlations between ACE SWA change scores (X-axis) and WM improvement (Y-axis)
(a) Frontal ACE PreBase SWA during SWS (r= .447, p= .012, α=.0154);
(b) Frontal ACE PrePost SWA during SWS (r= .560, p= .001, α= .0038);
(c) Central ACE PreBase SWA during SWS (r= .524, p= .003, α= .0077);
(d) Central ACE PrePost SWA during SWS (r= .455, p= .010, α=.0115).

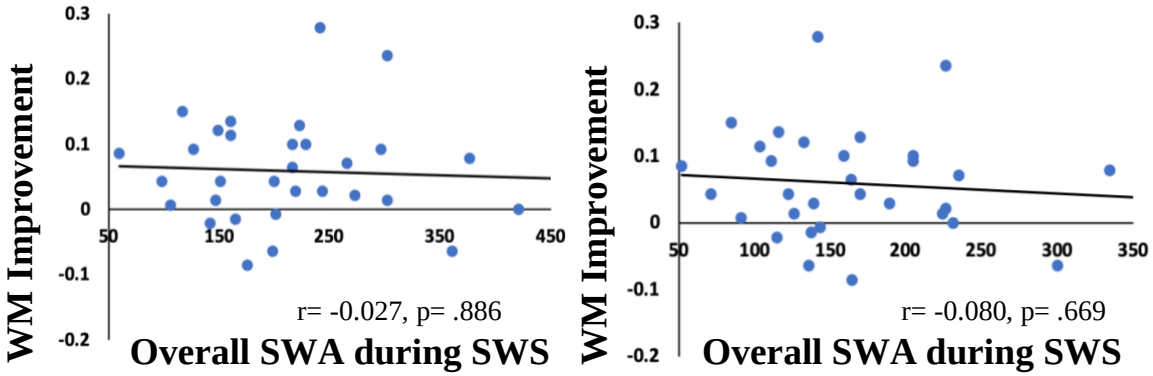


Figure 3.5 WM improvement not correlated with slow wave activity
Correlations between overall SWA power (X-axis) and WM improvement (Y-axis) (a) Frontal SWA during SWS (r= -0.027, p= .886); and (b) Central SWA during SWS (r= -0.080, p= .669).

Additionally, as predicted, we found no significant correlations between WM improvement and ACE sigma change scores (PreBase: all ps > .153; PrePost: all ps > .051) or overall sigma power (all ps > .237) during SWS. For Stage 2, no significant correlations between WM improvement and ACE SWA power were found for PreBase (all ps > .439) or PrePost (all ps > .619). Similarly, we found no significant correlations between WM improvement and ACE sigma change scores (PreBase: all ps > .672; PrePost: all ps > .257) or overall sigma power (all ps > .352) during Stage 2 sleep. Lastly, we found no significant correlations between WM improvement and RR_{HF} activity during Stage 2 sleep (p = .054) or SWS (p = .392).

Importance of ACEs for WM Improvement

Next, we assessed the relative importance for WM performance of ACE and non-ACE activity using hierarchical, linear regression. The regression results using frontal and central channels are shown in Table 3.6 a-b, respectively.

Regression Models using the Averaged Frontal Channel

In Model 1, WM gain was the dependent variable and Session 1 WM performance and overall frontal SWA in SWS were the independent variables. Model 1 reached significance ($F_{(2,29)}$= 4.798, p= .016; adj R^2 = .196), but adding the ACE measures (PrePost) in Model 2 enhanced the prediction of the model ($F_{(3,28)}$= 5.974, p= .021; adj R^2 = .325), with the ACE SWA (PrePost) being a significant predictor (p= .016). Model 2 accounted for significantly more of the variance in WM improvement than Model 1 (change in adj R^2 = .142, $F_{(1,28)}$= 6.504, p=.016). Similarly, adding the ACE SWA (PreBase) measures in Model 2 enhanced the prediction of the model ($F_{(3,28)}$= 4.319, p= .013; adj R^2 = .243), although non-significantly (change in adj R^2 = .068, $F_{(1,28)}$= 2.774, p=.106).

Regression Models using the Averaged Central Channel

In Model 1, baseline WM performance and overall central SWA in SWS were the independent variables. Model 1 reached significance ($F_{(2,29)}$= 4.796, p= .016; adj R^2 = .196), but adding the ACE SWA measures (PreBase) in Model 2 elevated significance of the model ($F_{(3,28)}$= 5.222, p= .005; adj R^2 = .290), with the ACE SWA (PreBase) being a significant predictor (p= .036). Again, Model 2 accounted for significantly more of the variance in WM improvement than Model 1 (change in adj R^2 = .147, $F_{(1,28)}$= 4.812, p=.036). Similarly, adding the ACE SWA measures (PrePost) in Model 2 elevated the model ($F_{(3,28)}$= 4.6, p= .009; adj R^2 = .258), although non-significantly (change in adj R^2 = .109, $F_{(1,28)}$= 3.411, p=.075).

In summary, while the overall SWA power did not predict individual differences in sleep-dependent WM gain, ACE events predicted up to 18.8% of the variance in performance improvement on this WM task.

Discussion

Consistent with Naji et.al (2019), we confirmed an autonomic cardiac event during NREM sleep that is temporally coupled with a significant boost in brain oscillations, and reported that these autonomic/central events (ACEs) contribute to WM improvement. Specifically, we showed that increases in the EEG amplitude in SWA and sigma bands preceded the large-amplitude HR bursts. Furthermore, we showed that these time-locked boosts in SWA during SWS, but not sigma or RRHF, can predict WM improvement across a daytime nap to a greater extent than overall SWA. Taken together, the results suggest that heart-brain interactions during sleep may be a critical mechanism for sleep-related WM gain.

Heart-brain interaction during sleep: findings and potential mechanisms

Emergent research examining brain-body communication suggests that autonomic activity may be linked with sleep brain activity, and that this interaction is likely a distinct predictor of plasticity, cognitive ability and enhancement. Studies have revealed a consistent symmetry between heart and brain activity with temporal changes in NREM delta (0.5-4Hz) power and ANS activity (Ako et al., 2003; Brandenberger et al., 2001a; Jurysta et al., 2003, 2005; Kuo & Yang, 2004; Rothenberger et al., 2015; Thomas et al., 2014; Yang et al., 2002). Delta EEG power, a marker of homeostatic sleep drive dissipates across successive NREM periods. Brandenberger and colleagues (2001) demonstrated an inverse coupling between oscillations in delta wave activity (0.5-3.5Hz) and autonomic activity during nighttime sleep. Using a cross-correlation approach, Thomas et al. (2014) showed a temporal relationship between SWA and high frequency cardiopulmonary (0.1-0.4Hz) coupling, an ECG-derived biomarker of stable sleep, during both stage 2 sleep and SWS. These findings suggest that CNS-ANS dynamics support the interdependency between cortical and cardiac function during sleep.

Several studies have attempted to provide insight on directionality and potential mechanisms of heart-brain communication, with some suggesting that vagal modulation may precede increases in EEG delta power (Jurysta et al., 2003, 2005) and some suggesting that the relationship may be more strongly driven by CNS than ANS activities (Rothenberger et al., 2015). Although more research is needed to understand the complicated relation between the ANS and CNS, one possible reason for the discrepancy regarding ANS-CNS coupling in previous work may be due to the method of averaging across large periods of the night that underestimate tight temporal interactions between the heart and brain. Traditional measures examine activity over 5-minute windows, which may average out fluctuations that occur in shorter time scales (e.g., heart rate bursts <5 sec). Building upon these findings, the current study adopted a high temporal precision time-domain analysis approach to the cardiac signal, which allowed for the identification of HR burst that lasted 4-5 seconds and predominated (~1 per minute) in NREM sleep. By focusing on beat-to-beat changes in sleep ECG/EEG, the current study attempted to demonstrate functional significance of ACE activity for cognitive processes.

While mechanisms driving EEG fluctuations time-locked on HR bursts remains unclear, some evidence points to arousal responses during sleep. In line with our findings, de Zambotti et al. (2016) showed that tone-triggered K-complexes are temporally coupled with a rapid increase and then decrease in heart rate activity, and coincide with bursts of K-complexes and slow waves (Sforza et al., 2000). In this context, both synchronous EEG (K-complexes, or bursts of SOs) and cardiovascular activations (heart-rate acceleration) were viewed as responses to arousal from sleep, as when acoustic tones were not accompanied by a K-complex, the heart rate fluctuation was reduced or absent, indicating that arousal responses might be driving ANS/CNS activities. It's been hypothesized that in the case of the K-complex, the recruited synchronized EEG response acts as a mechanism to decrease cortical arousal, suggesting that the heart-rate acceleration (tachycardia, or HR bursts) can be viewed as peripheral response of arousal from sleep. Taken together, the

subsequent heart-rate deceleration that de Zambotti et al. (2016) showed and the surge of HF that Naji et al. (2019) and the current study found may reflect a feedback effect of arousal showing an inertial effect once the arousal stimulus is removed. Alternatively, arousal and post-arousal periods may modulate the autonomic system reflecting the activation-deactivation of neuronal oscillations intrinsically regulated by the cyclic arousability of the sleepy brain (Schnall et al., 1999; Sforza et al., 1999; Ferri et al., 2000).

In addition to arousal responses, ANS-CNS coupling events may also represent the brainstem's dynamic maintenance of homeostasis during the transition from wake to sleep. As homeostatic pressure drives the transition from lighter sleep to deeper stages, the CNS and ANS experience large and rapid slowing in physiological rhythms, including decreased heart rate, broad synchronization of EEG slow waves (Fernandez Guerrero & Achermann, 2018), as well as alignment of cortical and autonomic signals (Ulke et al., 2017). Brainstem medullary nuclei are responsible for a wide range of bodily functions including deepening of slow wave sleep (Anaclet & Fuller, 2017) and deceleration of heart rate (Monge Argilés et al., 2000). It is, therefore, possible that medullary nuclei regulating wake to sleep transitions modulate the pace of the slow down with brief accelerations in cardiac activity. Due to the relative overlap between nuclei, these fluctuations may promote time-locked ACEs between sleep promoting oscillations such as SOs and spindles. Thus, ACE coupling may represent the adaptive and flexible modulation of central and peripheral activities by the brainstem. However, more research is needed to make definite conclusions. Regardless of mechanism, these interactions have an intriguing interplay with sleep-related cognitive plasticity.

Heart-brain interactions during sleep for cognition

Though the functional significance of CNS-ANS couplings during sleep is only beginning to be explored, we hypothesize that ACE activity may play an important role in hippocampal-

prefrontal cognitive enhancement. Results from our group have shown ACE (SWA and spindles) contributions to long-term, episodic memory (Naji et al., 2019), as well as WM gains (SWA, current study). In addition, recent studies implicate frontal SWA with improvement in WM, a cognitive ability strongly supported by the prefrontal cortex (Wager & Smith, 2003). For example, Ferrarelli et al. (2019) demonstrated that fronto-parietal SWA during nocturnal sleep can predict the WM improvement across the sleep. Similarly, Sattari et al. (2019) showed that frontal SWA, but not sigma, during a nap predicted WM improvement in older adults. Furthermore, ventromedial prefrontal cortex has been shown to regulate both vagal activity and slow oscillations (Dang-Vu et al., 2010; Thayer & Lane, 2000), and higher waking vagal activity is associated with better executive function (including WM). Anatomically, bidirectional projections from the prefrontal cortex to the hypothalamus and brainstem create a feedback loop for communication between peripheral sites and central cognitive areas (Shaffer et al., 2014; Thayer & Lane, 2009a). Furthermore, the prefrontal cortex is implicated in top-down control of the vagus nerve, and prefrontal cortical thickness is positively associated with vagally-mediated autonomic activity during wake in both young (Winkelmann et al., 2016) and older adults (Lin, Ren, et al., 2017). Together, these studies point to a significant role of prefrontal processing in the improvement of working and long-term memory during sleep that is mediated by autonomic activity.

The current study is the first, to our knowledge, to identify a functional role of ANS-coupled EEG fluctuations on WM improvement. Moreover, we find a high degree of specificity with ACE-SWA but not ACE-sigma or ACE-RR_{HF} benefitting performance. Both SWA and Sigma changes scores were significantly modulated by HR bursts, with the peak SWA occurring during the -5 window during both NREM stage 2 and SWS. However, only the SWA during SWS significantly predicted WM improvement. Indeed, SWS has been linked to synaptic plasticity and cortical reorganization (Tononi and Cirelli, 2003; Takashima et al., 2006; Dang-Vu et al., 2010), and is thought to play an important role in cerebral restoration and recovery (Horne, 1992), thereby making it a candidate

for facilitating WM improvement. In addition, the low levels of acetylcholine and catecholamines that exist SWS have been shown to facilitate the occurrence of synaptic depression (Harley, 1991; Seol et al., 2007). Furthermore, the most prominent EEG event during SWS, SWA has been considered to reflect localized, experience-dependent, cortical plasticity (Huber et al., 2004; Miyamoto et al., 2017; Rodriguez et al., 2016). Taken together, results in the current study were consistent with the previous literature that SWS might provide an optimal brain state that can be exploited to enhance WM changes.

It's noteworthy that the current study only showed an association between ACE SWA and WM improvement, but not overall SWA. Intrudingly, studies examining the association between SWA power during sleep and WM improvement showed mixed results. While some previous studies showed an association between SWA power during sleep and WM improvement (Ferrarelli et al., 2019; Pugin et al., 2015; Sattari et al., 2019), we and others (Lau et al., 2015b; MacDonald et al., 2018) failed to find a correlation between WM improvement and overall SWA. In fact, previous studies showing a positive association were either examined in a different age group (Sattari et al., 2019), or tested under different experimental design (Ferrarelli et al. 2019; Pugin et al. 2015). Specifically, Ferrarelli et al. (2019) tested WM and overnight sleep on two consecutive nights and showed that the increased SWA across the two nights were correlated with the WM improvement across the two days (measured with 1-Back accuracy). Similarly, Pugin et al. (2015) tested overnight sleep on two nights, separated by three weeks of WM training, and showed that the increased SWA across the two nights were correlated with the WM improvement (from pre-training to post training; measured with auditory N-back capacity). In contrast, previous studies that used similar pre-nap/ post-nap paradigm showed no effect of overall SWA (Lau et al., 2015b; MacDonald et al., 2018). The overall SWA might reflect the experience-dependent changes in the brain following a learning period, whereas the ACE SWA might reflect the adaptive prefrontal functioning that contributes to WM improvement. The current mechanism underlying the role of

SWA on WM remain unclear. We suggested that adding ACE analysis to future studies will be critical for understanding potential sleep mechanisms for WM improvement.

Our data suggest that robust coupling between frontal SWA and HR reflects increased functioning of prefrontal cortex during NREM sleep, including benefits to WM and long-term memory. This hypothesis is consistent with the neurovisceral integration model (Thayer and Lane, 2000) that contends that medial prefrontal cortex regulates autonomic activity through its connections with the nucleus tractus solitarii (NTS), and proposes that autonomic activity reflects the functional capacity of the brain structures that support WM and physiological self-regulation (Thayer et al., 2009). These findings suggest the intriguing possibility that modulation of autonomic activity during sleep may provide a novel method for boosting executive function. Vagal nerve stimulation, for example, has been considered a valuable therapeutic option for neurologic diseases, and studies have demonstrated the ability of vagal nerve stimulation during wake to modulate vagal afferents activation (Nonis et al., 2017), and to enhance verbal memory performance (Clark et al., 1999), cognitive flexibility (Ghacibeh et al., 2006), and recently, WM (Sun et al., 2017). Future research should investigate the potential benefit of sleep-related interventions (i.e. non-invasive brain stimulation and vagal nerve stimulation) on heart-brain communication and its potential benefit for cognitive enhancement or as a clinical intervention in age-related cognitive decline.

Chapter Four: Competitive dynamics underlie cognitive improvements during sleep

Abstract

We provide evidence that human sleep is a competitive arena where cognitive domains vie for limited resources. Using pharmacology and effective connectivity analysis, we demonstrate that long-term memory and working memory are served by distinct offline neural mechanisms that are mutually antagonistic. Specifically, we administered zolpidem to increase central sigma activity and demonstrated targeted suppression of autonomic vagal activity. With effective connectivity, we determined the central activity has greater causal influence over autonomic activity, and the magnitude of this influence during sleep produced a behavioral trade-off between offline long-term and working memory processing. These findings show the first evidence of a slow oscillation switch mechanism that toggles between central sigma-dependent long-term memory and autonomic vagal-dependent working memory processing.

Introduction

Working memory (WM) and long-term memory (LTM) serve separate functions and the idea that they are supported by separate systems has become a core assumption of modern cognitive psychology (James, 1890). WM is a control process for planning and carrying out behavior that is information-independent, whereas LTM is an information-dependent vast store of knowledge and record of prior events. Both WM and LTM rely on offline periods that include sleep to facilitate performance improvement. According to the framework of systems consolidation, long-term memories are initially bound by a fast-learning system in the hippocampus (i.e. encoding), followed by stabilization of these memory traces in cortical stores (i.e., consolidation). Non-rapid-

eye-movement (NREM) sleep may facilitate consolidation by increasing communication between cortico-thalamo-hippocampal circuits via nested oscillations of slow oscillations (<1Hz, SO), spindles (sigma power; 12-15Hz), and sharp wave ripples (SPW-R), respectively (Latchoumane et al., 2017; Niethard et al., 2018; Rasch & Born, 2013). SOs reflect fluctuations of the membrane potential and orchestrate transitions from neuronal silence (hyperpolarized downstates) to neuronal excitation (depolarized upstates). Spindles, nested in SO upstates, gate dendritic Ca2+ influx and promote synaptic plasticity. Hippocampal SW-Rs nested in spindles are closely linked to the reactivation of cell assemblies engaged during encoding. Prior studies suggested that spindles may initiate hippocampal-cortical dialogue by grouping SW-Rs, which facilitates information transfer between neocortical and hippocampal cell assemblies. In humans, pharmacological interventions that boost spindle activity enhance sleep-dependent hippocampal LTM, measured by the paired-associates task (Mednick et al., 2013; Wamsley et al., 2013; Zhang et al., 2020).

Classic models of WM propose two governing mechanisms: 1) an active maintenance of information online through the elevated firing of prefrontal neurons, and 2) a supervisory executive control process that is supported by a prefrontal-subcortical inhibitory network (Compte et al., 2000; Funahashi et al., 1993). Due to innervations to the heart via sympathetic stellate ganglia and parasympathetic vagal nerve efferents, cardiac autonomic activity is thought to reflect functioning of prefrontal inhibitory processing (Thayer et al., 2009). Accordingly, vagally-mediated, high frequency heart rate variability (0.15-0.40, HF HRV) during wake correlates with executive function tasks, such as WM, which rely on PFC activity (Mosley et al., 2018). Improvement in WM, however, only occurs when the interval between training sessions contains a period of sleep, measured by N-back, complex-span task, and digit span (Ferrarelli et al., 2019; Kuriyama et al., 2008a; Sattari et al., 2019; Scullin et al., 2012; Zinke et al., 2014). Although the exact mechanisms of WM improvement during sleep are still not entirely understood, prior studies point to SWS as an optimal state for synaptic plasticity and cortical reorganization. During SWS, vagal activity is also at its highest

compared to all other states of consciousness (Trinder et al., 2001). Building on this foundation, a recent study identified vagal HF HRV during SWS as a strong predictor of WM improvement, measured by the operation-span task (Chen, Whitehurst, Naji, et al., 2020a).

Together, theoretical models and empirical data suggest that NREM sleep may facilitate improvement in WM via strengthening of prefrontal-autonomic inhibitory networks, measured by HF HRV, while facilitating the formation of LTM via thalamic spindles driving the hippocampal-cortical dialogue, measured by sigma power. The question is how the sleeping brain performs both of these complex feats and which sleep features are associated with these processes? Prior animal studies suggest a potentially antagonistic interplay between the cortico-thalamo-hippocampal networks and the prefrontal-autonomic inhibitory networks (Logothetis et al., 2012; Novitskaya et al., 2016). However, this possibility and its functional significance has not been studied in humans.

In the present study, we enacted a pharmacological strategy to investigate the bi-directional interplay between central (reflected in sigma activity) and autonomic (reflected in vagal HRV) activities during overnight sleep and its impact on LTM and WM, measured by the word-paired associative task and the operation-span task. Specifically, we tested our model that central sigma activity would suppress autonomic vagal activity using effective connectivity (Friston, 2011), defined as the influence that one neural system exerts over another, which can be estimated using Granger causality (Figure 4.3a). We identified a novel antagonistic relationship between sigma and vagal activity during sleep, with the degree of mutual antagonism between sigma and vagal activity predicting a heretofore unreported behavioral trade-off between LTM and WM. These results suggest that NREM sleep confers benefits to WM and LTM by switching between separate offline mechanisms, i.e., the prefrontal-autonomic inhibitory processing and the hippocampal-cortical dialogue. Furthermore, this slow oscillation switch can be biased towards LTM consolidation by increasing sigma activity, in this case pharmacologically, and presumably by other methods as well. These results illuminate the dynamics interplay underlying LTM and WM processes during sleep.

Methods

Participants

34 adults in experiment 1 (M_{age} = 20.88 ± 1.88 years, 17 Females) and 38 adults in experiment 2 (M_{age} = 20.85 ± 2.97 years, 19 Females) with no history of neurological, psychological, or other chronic illnesses were recruited for the study (Table 4.1 demographics). All participants signed informed consent, which was approved by the Western Institutional Review Board and the University of California, Riverside Human Research Review Board. Exclusion criteria included irregular sleep/wake cycles; sleep disorder; personal or familial history of diagnosed psychopathology; substance abuse/dependence; loss of consciousness greater than 2 minutes or a history of epilepsy; current use of psychotropic medications; and any cardiac or respiratory illness that may affect cerebral metabolism, which was determined during an in-person psychiatric assessment with trained research personnel. Additionally, all participants underwent a medical history and physical appointment with a staff physician to ensure their physical well-being. All subjects were naive to or had limited contact with (<2 lifetime use and no use in last year) the medication used in the study. Participants were asked to refrain from consuming caffeine, alcohol, and all stimulants for 24 h prior to and including the study day. Participants filled out sleep diaries for one week prior to each experiment and wore wrist-based activity monitors the night before the study (Actiwatch Spectrum, Philips Respironics, Bend, OR, USA) to ensure participants were well-rested (at least 7 hours per night during the week including the eve of the experimental day). Participants received monetary compensation and/or course credit for participating in the study. Study procedures were illustrated in Figure 4.1.

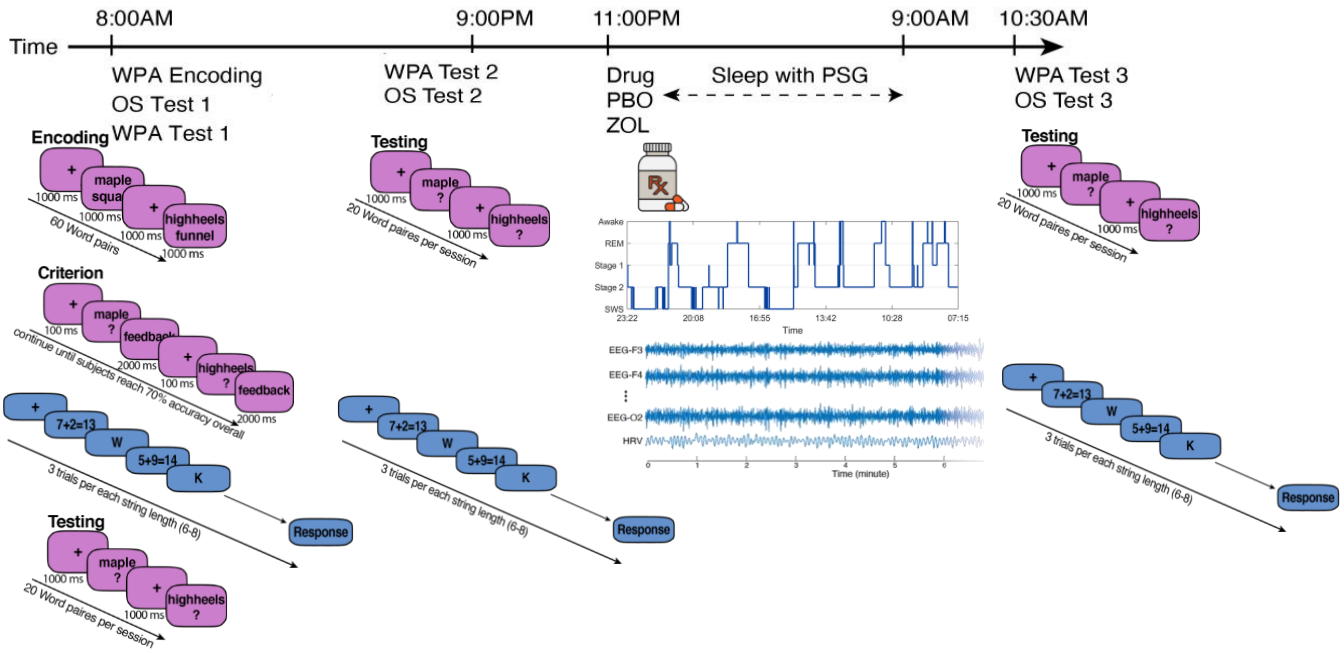


Figure 4.1 Experimental design and behavioral tasks

Experiment 1: Participants reported to the lab at 9:00PM and were hooked up to polysomnography (PSG), including electroencephalography (EEG), electrocardiogram (ECG), electromyogram (EMG), and electrooculogram (EOG). Before sleep, we recorded 5-min resting HRV while subjects lay awake in a still, supine position. At 11:00PM, directly before lights-out, subjects ingested either 10mg of zolpidem or placebo. Sleep was monitored online by a trained sleep technician. Participants were woken up at 9:00AM the next morning and permitted to leave the lab. Each participant experienced two visits per drug condition (a total of four visits).

Experiment 2: At 8:00AM, participants began encoding for the episodic memory word-paired-associates (WPA) task, followed by the working memory operation-span task (OS) task and immediate recall for the WPA (Test 1). Participants left the lab after cognitive testing. Participants were asked not to nap, exercise, or consume caffeine or alcohol, and were monitored with actigraphy during the break. Participants returned to the laboratory at 9:00 PM to complete the delayed recall over wake for WPA and OS (Test 2). Participants were then hooked up to polysomnography (PSG), including electroencephalography (EEG), electrocardiogram (ECG), electromyogram (EMG), and electrooculogram (EOG). Before sleep, we recorded 5-min resting HRV while subjects lay awake in a still, supine position. At 11:00PM, directly before lights-out, subjects ingested either 10mg of zolpidem or placebo. Sleep was monitored online by a trained sleep technician. Participants were woken up at 9:00AM the next morning and provided a standardized breakfast. At 10:30 AM, participants completed the delayed recall over sleep for WPA and OS (Test 3). For both tasks, to assess the change in performance, we measured two difference scores: overnight change (Test 3 – Test 2); 24-hr change (Test 3 – Test 1). Each participant experienced one visit per drug condition (a total of two visits).

Data Reduction

Experiment 1

25 participants completed 4 visits (2 placebo nights and 2 zolpidem nights), 8 participants completed 2 visits (1 placebo night and 1 zolpidem night), 1 participant completed a zolpidem visit, due to scheduling conflicts. Therefore, 56 placebo and 59 zolpidem nights were included in the analyses.

Experiment 2

36 participants completed the placebo night, and 35 participants completed the zolpidem night PSG recordings. 35 participants completed all three sessions of operation-span (working memory) task in both placebo and zolpidem conditions. 33 participants completed all three sessions of word-paired associates (long-term memory) task in both placebo and zolpidem conditions.

Sleep Recording

EEG data were acquired using a 32-channel cap (EASEYCAP GmbH) with Ag/AgCI electrodes placed according to the international 10-20 System (Jasper, 1958). 22 electrodes were scalp recordings and the remaining electrodes were used for electrocardiogram (ECG), electromyogram (EMG), electrooculogram (EOG), ground, an online common reference channel (at FCz location, retained after re-referencing), and mastoid (A1 & A2) recordings. The EEG was recorded with a 1000 Hz sampling rate and was re-referenced to the contralateral mastoid (A1 & A2) post-recording. Data were pre-processed using BrainVision Analyzer 2.0 (BrainProducts, Munich Germany). Eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, O2), the EMG, and EOG were used in the scoring of the nighttime sleep data. High pass filters were set at .3 Hz and low pass filters at 35 Hz for EEG and EOG. Raw data were visually scored in 30-sec epochs into Wake, Stage 1,

Stage 2, Slow Wave Sleep (SWS) and rapid eye movement (REM) sleep according to the Rechtschaffen & Kales' manual using HUME, a custom MATLAB toolbox. After staging, all epochs with artifacts and arousals were identified rejected by visual inspection before spectral analyses. Minutes in each sleep stage and sleep latencies (SL) (the number of minutes from lights out until the initial epoch of sleep, Stage 2, SWS and REM) were calculated. Additionally, wake after sleep onset (WASO) was calculated as total minutes awake after the initial epoch of sleep, and sleep efficiency (SE) was computed as total time spent asleep after lights out (~11:00PM) divided by the total time spent in bed (~11:00PM-9:00AM) * 100. Sleep architectures were reported in Table 4.2a and 4.2b.

Heart Rate Variability

Electrocardiogram (ECG) data were acquired at a 1000-Hz sampling rate using a modified Lead II Einthoven configuration. We analyzed HRV of the R-waves series across the whole sleep/wake period using Kubios HRV Analysis Software 2.2 (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Finland), according to the Task Force guidelines [57]. RR peaks were automatically detected by the Kubios software and visually examined by trained technicians. Incorrectly detected R-peaks were manually edited. Missing beats were corrected via cubic spline interpolation. Inter-beat intervals were computed, and a third-order polynomial filter was applied on the time series in order to remove trend components. Artifacts were removed using the automatic medium filter provided by the Kubios software.

The HRV analysis of the RR series was performed by using a Matlab-based algorithm. An autoregressive model (Model order set at 16) was employed to calculate the absolute spectral power (ms2) in the LF HRV (0.04–0.15 Hz; ms2) and the HF HRV (0.15–0.40 Hz; ms2; an index of vagal tone) frequency bands, as well as total power (TP; ms2; reflecting total HRV), and HF peak frequency (HFpf; Hz; reflecting respiratory rate). From these variables, we derived the HF

normalized units (HF_{nu} = HF[ms^2]/HF[ms^2]+LF[ms^2]) and the LF/HF ratio (LF[ms^2]/HF[ms^2]), an index often considered to reflect the sympathovagal balance (i.e., the balance between the two branches of the ANS), but whose meaning has been recently put into question. The LF, HF, and TP measures had skewed distributions and as such were transformed by taking the natural logarithm. Since the LF normalized units are mathematically reciprocal to HF_{nu} (i.e. LF_{nu} =1- HF_{nu}), to avoid redundancy, only the HF_{nu} index is computed, an index often thought to reflect vagal modulation. Due to controversies about the physiological mechanisms that contribute to changes in LF activity, LF, LF/HF ratio and HFnu are difficult to make for these parameters, but they are reported for descriptive purposes.

In addition to the frequency domain parameters, RMSSD (ms; root mean square of successive differences) was calculated as a measure of vagally-mediated HRV in the time-domain. Similar to the frequency adjustments, to adjust for skewed distributions in the RMSSD, we report the natural logarithm. Additionally, RR (ms; time interval between consecutive R-peaks, reflecting frequency of myocardial contraction) were calculated as an index of cardiac autonomic control in our analyses.

For time-domain and frequency-domain HRV measures during different sleep stages, consecutive artifact-free 5-min windows of undisturbed sleep were selected across the whole night using the following rules: (a) the 1.5-min preceding, and (b) the entire 5-min epoch selected must be free from stage transitions, arousal, or movements. Windows were identified and averaged within Stage 2 sleep, slow-wave sleep (SWS), and REM sleep. We also analyzed 5 min of pre-sleep wakefulness (Rest). Epochs of N1 were not analyzed. All the HRV parameters by drug condition and sleep stage were reported in Supplemental Table 4.3a-c.

Power spectral analysis

The EEG power spectrum was computed using the Fast Fourier Transformation. SWA (0.5-2Hz), delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), sigma (12-15Hz), beta (15-30Hz), and total power (0.3-35Hz) were calculated for each sleep stage (Stage 2, SWS and REM). The EEG epochs that were contaminated by muscle and/or other artifacts were rejected using a simple out-of-bounds test (with a ±200 μV threshold) on high-pass filtered (0.5 Hz) version of the EEG signals. Then, the normalized power spectra (% power of each frequency band of interest/ total power) were averaged bilaterally within each sleep condition/stage/subject. Power analyses that showed significant drug effect were reported in Table 4.4a-b.

Effective Connectivity

To explore the causal information flow between CNS and ANS sleep features, we considered sigma to reflect CNS activity and HFln to reflect ANS activity. Sigma power of eight EEG channels (F3, F4, C3, C4, P3, P4, O1, O2) and HF of HRV were considered as signals to estimate effective connectivity. To adopt uniform timing across signals and avoid temporal misalignments between EEG signals and HF time series, a sliding window technique was incorporated with window length of 5 minutes and stride of 5 seconds. All data during nighttime sleep was used to have continuous time series of Sigma powers and HF, and length of 5 minutes was selected to be consist with HRV process. Therefore, for each subject, nine different signals were constructed including ratio of Sigma power band to total power of EEG of eight channels and HF power of HRV for each five-minute window (see Figure 4.3a).

Generalized partial direct coherence (GPDC) measure was used to estimate causal information flow between Sigma power and HF. GPDC uses multivariate vector autoregressive

(MVAR) model to model causal interactions between signals and estimate directed causal information flow between signals by using the coefficients and parameters of MVAR.

After constructing Sigma power and HF signals, GPDC was computed for each window with length of 500 samples (500 * 5 s = 2500 s) with stride of 250 samples. First, signals interactions were modeled by MVAR model (Eq. 1).

(1)

$$X(n) = \sum_{k=1}^{p} A_k X(n-k) + w(n)$$

Where $X(n)$ is the vector of signal values (with length of N, the number of signals, $N = 8$) in time n, $X(n) = [x_1(n), x_2(n), \dots, x_N(n)]^T$. p is order of the MVAR model which was selected according to Akaike criterion (AIC), $p = 4$. A_k is the matrix of MVAR coefficients and each element, $a_{ij}(k)$, stands how much j-th signal in time $n-k$ affects i-th signal in time n and $w(n)$ is the vector of model's additive Gaussian noise with zero mean and covariance matrix Σ. After modeling the interaction of the signals, GPDC was computed using frequency domain of coefficients and covariance matr

(2)

$$\bar{\pi}_{ij}(f) = \frac{\frac{1}{\Sigma_{ii}} A_{ij}(f)}{\sqrt{\sum_{k=1}^{N} \frac{1}{\Sigma_{kk}^{\,2}} \left|A_{kj}(f)\right|^2}}$$

consequently:

(3)

$$0 \le \left|\bar{\pi}_{ij}(f)\right|^2 \le 1$$

And

(4)

$$\sum_{i=1}^{N} \left|\bar{\pi}_{ij}(f)\right|^2 = 1$$

$\bar{\pi}_{ij}(f)$ is the estimated matrix of causal information flow and the j-th column represent causal information outflow from the j-th signal to all the other signals. Average values over frequencies were considered for further process and based on the main purpose of the study two quantifier were defined as follow (see Figure 4.3a):

1. Causal information outflow from HF to all EEG channels, $HF_{Outflow}$ – Average (n=8) of causal information flow from HF to EEG sigma activity. $HF_{Outflow}$ represents the strength of causal effect of HF to Sigma power.
2. Causal information inflow to HF from all EEG channels, HF_{Inflow} – Average (n=8) of causal information flow from EEG sigma activity to HF. HF_{inflow} represents the strength of causal effect of Sigma to HF.
3. Effective connectivity ratio: HFInflow over HFOutflow, where greater numbers represented a greater central sigma control over autonomic vagal activity than vice versa.

Sigma/SO Coupling

Slow oscillations (SO) trough were detected for each channel automatically using the algorithm introduced by Dang-Vu et al. [58]. For each SO, the sigma power spectrum (12-16 Hz) was computed in the time margin of SO trough to 1s post SO trough. To access SOs which were coupled with Sigma waves, the median of all normalized Sigma power of SOs for all recording was computed for each channel. The SOs which had Sigma power greater than the median values in each quartile was considered as the SO-Sigma coupled and the number of coupled SOs was considered to further statistical analysis.

Statistical Analyses

All statistical analyses were performed in R 3.6.2, using the libraries lme4 and lsmeans. P-values less than 0.05 were considered significant; p-values between 0.05 and 0.07 were considered trend-significant; p-values greater than 0.07 were considered non-significant. We used a linear mixed model (LMM) to evaluate the effects of zolpidem on sleep architecture, EEG power spectrum, autonomic profiles, and behavioral improvements. LMMs were chosen because it allows modeling of random effects and allow for the intercept and slope to be correlated [59]. LMMs are parametric

models that use Maximum Likelihood Estimates (MLE) to obtain coefficients and covariance structures. LMMs do not depend on limited assumptions about variance-covariance matrix assumptions (sphericity). Additionally, LMMs allow inclusion of an unbalanced number of observations per participants in the analyses. Moreover, LMMs models take into account the influence of factors whose levels are extracted randomly from a population (i.e. participants), thus yielding more generalizable results.

Sleep architecture and Power spectrum

Using LMMs, we tested for the main effect of drug condition for sleep architecture (see Table 4.2), EEG power spectrum (see Table 4.4).

Autonomic Profiles

For autonomic profiles, we tested for the main effect of drug condition and interactions between sleep stage and drug condition by approximating likelihood ratio tests (LRT) to compare LMMs with and without the effect of interest . We first built a reduced (nested) model, with sleep stage as the only effect, and then included drug condition as a fixed effect in the full model. By comparing the reduced and full model using the LRT, we can interpret if drug condition significantly modulated the outcomes. Tukey's correction for multiple testing was used for post-hoc comparisons.

Effective Connectivity

Using LMMs, we tested for the main effect of drug condition, the main effect of inflow vs outflow, and interaction between the two factors *(*see *Figure 4.3b 4.3c)*. We first built a reduced (nested) model, with inflow vs outflow, as the only effect, and then included drug condition as a fixed effect in the full model. By comparing the reduced and full model using the LRT, we can

interpret if drug condition significantly modulated the outcomes. Tukey's correction for multiple testing was used for post-hoc comparisons.

Behavioral Tasks

To investigate the drug effect on cognitive enhancement, LMMs were used with the drug condition as the predictor of interest (fixed effect), the improvement in WPA and OS tasks as outcome variables, and participants as crossed random effects. As we assume larger individual differences of improvement and difference in improvement between drug conditions, our LMMs include both a random intercept and a random slope term. To account for practicing effect on the tasks, we included visit and baseline performance as a covariate in the models. We first confirmed no differences at baseline (Test 1) between the placebo and zolpidem visits. Next, we confirmed no differences of improvements across 12-hr of waking (Test 2 – Test 1) between the placebo and zolpidem visits. We then tested the sleep-dependent changes in improvement: the overnight (Test 3 – Test 2) and 24-hr (Test 3 – Test 1) changes (see Figure 4.4a 4.4b). Again, we tested for the effect of drug condition by approximating LRTs.

Correlations

Lastly, we used a Pearson's correlation coefficients to examine the functional roles of sigma, vagal activity, and causal information flow on sleep-dependent behavioral changes. We further used the Fisher r-to-z transformation to compare the differences between two correlations of interests.

Results

Experiment 1.

Based on previous findings, we predicted that central sigma power would have an inhibitory effect on cardiac vagal tone. To this end, we administered zolpidem in a double-blind,

placebo-controlled, randomized cross-over design, in which each participant experienced two nights per drug condition (zolpidem or placebo; a total of 4 nights; N = 34; Mage = 20.88 ± 1.88 years, 17 Females), with EEG and ECG monitored (Figure 4.1 shaded area). The order of drug conditions was counterbalanced with at least a one-week interval between the experimental visits to allow for drug clearance. We performed power spectral analysis to quantify normalized sigma activity and analyzed HRV profiles. Our intervention was successful, whereby zolpidem increased time spent in SWS while decreasing WASO (Supplemental Table. S2), and enhanced sigma activity during stage 2 sleep (central channels: t = 2.112, p = .0349; parietal channels: t = 2.214, p = .0270, corrected by Tukey's multiple comparisons; Table 4.4), consistent with prior literature.

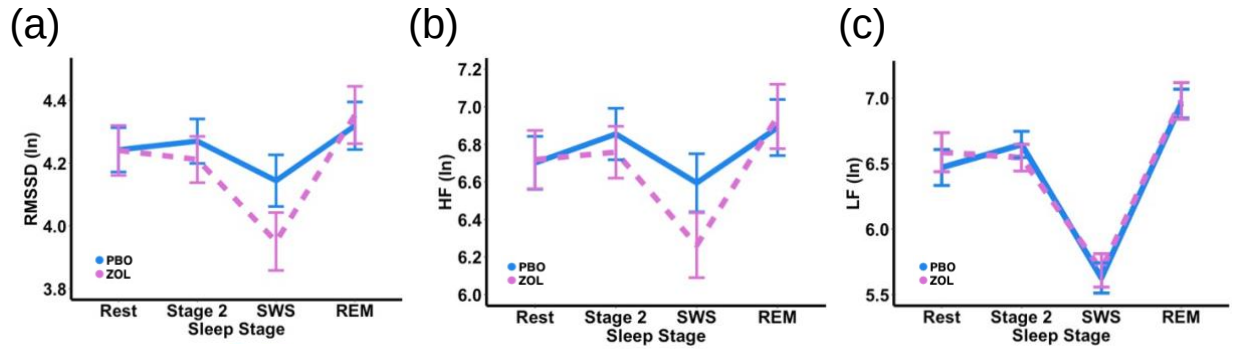


Figure 4.2 Zolpidem decreased vagally-mediated HRV, but not LF, during SWS

(a) RMSSD: We report a significant main effect of sleep stage ($F(3, 366) = 21.257$, $p < .0001$), with a decreased HRV during SWS compared to Rest, Stage 2, and REM (all ps < .0001). We also found a significant interaction ($F(3, 366) = 3.8630$, $p = .0096$) between sleep stage and drug condition, with decreased vagal activity during SWS ($p = .0006$) in zolpidem compared with placebo, but not during Stage 2 ($p = .3549$), REM ($p = .3804$), or Rest ($p = .6152$). The likelihood ratio test was significant (LR = 13.8544; $p = .0078$), suggesting that zolpidem significantly modulated the time-domain measure of HRV.

(b) High-frequency (HF) HRV: We report a significant main effect of sleep stage ($F(3, 366) = 16.9891$, $p < .0001$), with a decreased HRV during SWS compared to Rest ($p = .0006$), Stage 2 ($p < .0001$), and REM ($p < .0001$). Similarly, we also report a significant interaction ($F(3, 366) = 3.1899$, $p = .0238$) between sleep stage and drug condition, with decreased vagal activity during SWS ($p = .0020$) in zolpidem compared with placebo, but not during Stage 2 ($p = .4194$), REM ($p = .4365$), or Rest ($p = .6070$). The likelihood ratio test was significant (LR = 11.3671; $p = .0227$), suggesting that zolpidem significantly modulated the frequency-domain measure of HRV.

(c) Low-frequency (LF) HRV: We report a significant main effect of sleep stage ($F(3, 366) = 93.0330$, $p < .0001$), with a decreased LF power during SWS compared to Rest, Stage 2, and REM (all ps < .0001), and an increased LF power during REM compared to Rest and Stage 2 (all ps < .0001). No significant main effect of drug condition ($p = .6337$), nor interaction between sleep stage and drug condition ($p = .5681$) were found. The likelihood ratio test was not significant (LR = 2.2889; $p = .6828$), suggesting that zolpidem did not significantly modulate low frequency HRV.

As we hypothesized, zolpidem not only increased sigma activity, but also selectively suppressed vagal tone during sleep, measured by root mean square of the successive differences (RMSSD) (Figure 4.2a) and high-frequency HRV (HF; Figure 4.2b), but had no impact on low-frequency HRV (0.04-0.15, LF; Figure 4.2c). Other HRV indices were reported in Table 4.3.

We then tested our hypothesis that central sigma power would exert greater causal influence over vagal autonomic activity than the influence of vagal over sigma activity, and such difference would be increased by zolpidem. To test this prediction, we used effective connectivity estimation (Figure 4.3a). In particular, we tested the hypotheses that central sigma naturally exercises greater causal influence on autonomic vagal activity than vice versa in the placebo condition, and that increasing sigma with zolpidem would increase causal information flow from sigma to vagal activity, while decreasing the causal information flow from vagal to sigma activity in the zolpidem condition. For each subject, we calculated two measures: HFInflow and HFOutflow, respectively (see Methods). We confirmed our hypothesis that central sigma power exerted greater flow on vagal activity than vice versa in the placebo condition ($p < .0001$; Figure 4.3b). We also confirmed that such difference was increased by zolpidem ($p = .0369$; Figure 4.3b). Next, we calculated a composite score, the effective connectivity ratio: HFInflow over HFOutflow, where higher numbers represented greater central sigma control over autonomic vagal activity. We observed a higher effective connectivity ratio during the zolpidem night ($p = .0059$). Taken together, results from Experiment 1 were consistent with our hypotheses that central sigma activity naturally exerts dominance over autonomic activity during NREM sleep, and that increasing sigma activity via zolpidem inhibits vagal activity and enhances central sigma control over autonomic vagal activity.

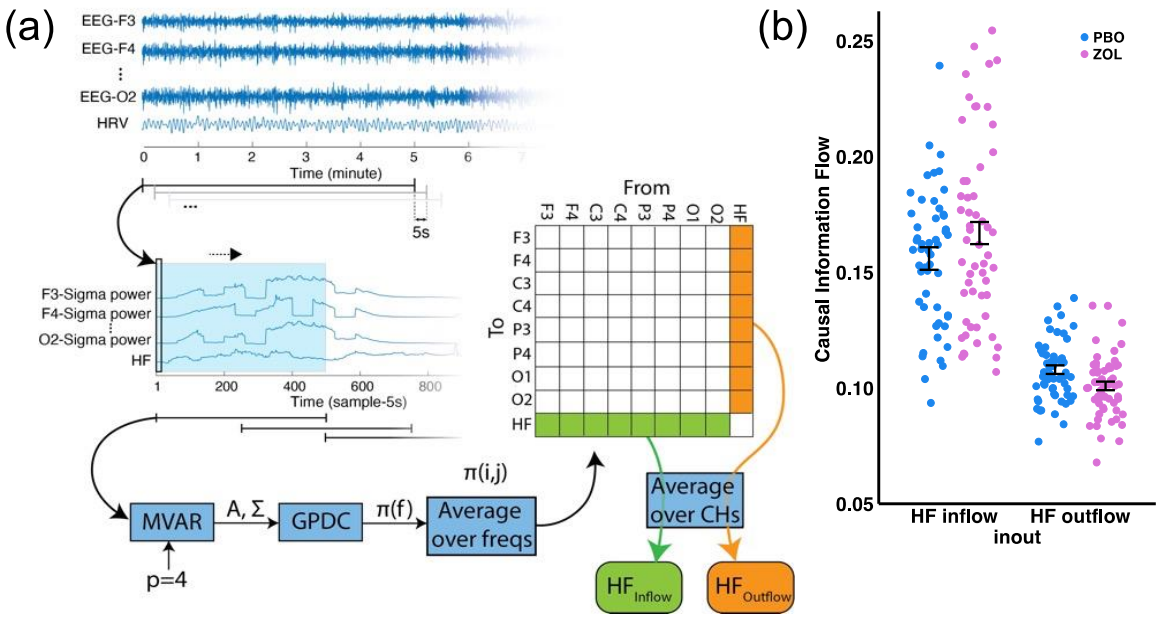


Figure 4.3 Effective Connectivity Modulated by Drug Condition

(a) Effective Connectivity Estimation Procedure (see Methods for details): Prior research using functional connectivity analysis has measured temporal similarity or correlations between different EEG channels. Although functional connectivity can reveal important information about communication, it is limited to correlational measures, and cannot identify directional causal communication. In contrast, Effective connectivity is defined as the influence that one neural system exerts over another either directly or indirectly, which can be estimated using Granger causality. According to Granger causality, a causal relation is detected if past values of a source signal help predict a second signal (sink signal) beyond the information contained in its past alone. Granger causality and causal information flow can be quantified using a multivariate vector autoregressive model (MVAR) and then examining the coefficients of the fitted model. Partial directed coherence (PDC) quantifies direct causal information outflow from each signal to all other signals, emphasizing the sinks, rather than the sources. The current study adopted the generalized form of PDC (GPDC) to quantify causal information flow with respect to both the source and the sink regions. Model order (p) of the MVAR model was the only parameter and was selected based on the Akaike information criterion (AIC).

(b) Experiment 1 Effective Connectivity: We report a main effect of inflow vs outflow ($F(1, 185) = 273.317$, $p < .0001$), with a greater HFinflow than HFoutflow in both drug conditions; an interaction between drug condition and inflow vs outflow ($F(1, 185) = 5.744$, $p = .0175$), with a greater HFinlfow during zolpidem compared to placebo ($p = .0369$). No main effect of drug condition was found ($F(1, 185) = 0.512$, $p = .4751$). The likelihood ratio test was significant ($LR = 6.0745$; $p = .0480$), suggesting that zolpidem significantly modulated the causal information flow between sigma and HF activity. Effective connectivity ratios (HFInflow/ HFOutflow) increased significantly during the zolpidem night ($F(1, 79) = 8.0607$, $p = .0059$).

Experiment 2.

In an independent sample of participants (N = 38; Mage = 20.85 ± 2.97 years; 19 Females), we added a behavioral experiment (Experiment 2; Figure 4.1) to the original design of Experiment 1 to test whether we could replicate the physiological results of Experiment 1 and determine their functional importance for sleep-dependent cognition. Again, we exploited zolpidem to modulate the interaction between central sigma and autonomic vagal activity and examined its impacts on the improvements of LTM and WM (Figure 4.1). The order of drug conditions was counterbalanced with at least a one-week interval between the two experimental visits to allow for drug clearance. The goal of experiment 1 was to thoroughly describe the physiological phenomenon across the whole night, whereas the goal for experiment 2 was to examine the functional impact of the pharmacological intervention on performance. For this reason, in experiment 2 we divided the night into quartiles and focused our analyses on quartile two and three combined to maximize zolpidem's effect, due to the pharmacodynamics of zolpidem, which has a half-life of (1.5–4.5 h), and onset (mean Tmax 1.6h). We hypothesized that sigma-guided vagal suppression effects would result in parallel behavioral effects with greater long-term memory and reduce improvement in working memory. We further hypothesized that the magnitude and the direction of causal information flow between central and autonomic systems would be correlated with the trade-off between LTM and WM.

The physiological results across one night of sleep in Experiment 2 were consistent with those from two nights of sleep in Experiment 1 (see Table 4.2 for sleep architecture; Table 4.4 for power spectrum; Table 4.3 for HRV). We confirmed that zolpidem increased sigma activity during sleep while suppressing vagal tone, measured by RMSSD and HF, but had no impact on LF. Similarly, we replicated the effective connectivity results (Figure 4.3c), in which zolpidem increased effective connectivity ratio ($p = .0265$), indicating greater causal influence of central sigma activity on autonomic vagal activity.

We further assessed the functional roles of each physiological measure (EEG sigma activity, cardiac vagal activity, and effective connectivity ratio) on LTM and WM changes across sleep. We hypothesized that increasing sigma activity would benefit LTM retention in a word-pair-associates (WPA) task, whereas decreasing vagal activity would hinder WM improvement on a working memory operation span (OS) task. To this end, we examined overnight and 24-hr change scores in each task between the two drug conditions. For the word-pair task, our analysis showed that zolpidem significantly increased 24-hr LTM retention (Figure 4.4a right panel) and overnight retention (Figure 4.4a left panel). For the working memory operation span task, our analysis demonstrated that zolpidem decreased overnight improvement (Figure 4.4b left panel) and 24-hr improvement (Figure 4.4b right panel), compared to placebo. In summary, we confirmed our behavioral hypothesis that sigma-guided vagal suppression would increase LTM (Figure 4.4a) and decrease WM improvement (Figure 4.4b).

Next, we tested the correlations between each physiological measure (EEG sigma activity, cardiac vagal activity, and effective connectivity ratio) and memory changes across sleep using Pearson's correlation coefficients. We found a functional dissociation in vagal activity and behavior, where vagal activity during SWS was negatively correlated with LTM in the zolpidem condition (24-hr retention and HFln: $r = -.460$; $p = .018$; Figure 4.4c right panel), and positively correlated with WM improvement (overnight retention and HFln: $r = .422$; $p = .032$; Figure 4.4c left panel) in the placebo condition. We compared correlations between HFln and LTM versus HFln and WM, and the difference was significant ($Z = 3.67$; $p = 0.0001$). This result is in line with our expectation that vagal activity during sleep differentially supports LTM and WM. Correlational statistics between vagally-mediated HRV parameters and behavioral improvements are shown in Table 4.5. No significant correlations were found between EEG sigma activity and WM improvement (zolpidem: all ps > .5687; placebo: all ps > .1943) or between EEG sigma activity and LTM retention (zolpidem:

all ps > .15516; placebo: all ps > .1383). Taken together, vagal activity was positively associated with WM improvement, but inversely related to LTM.

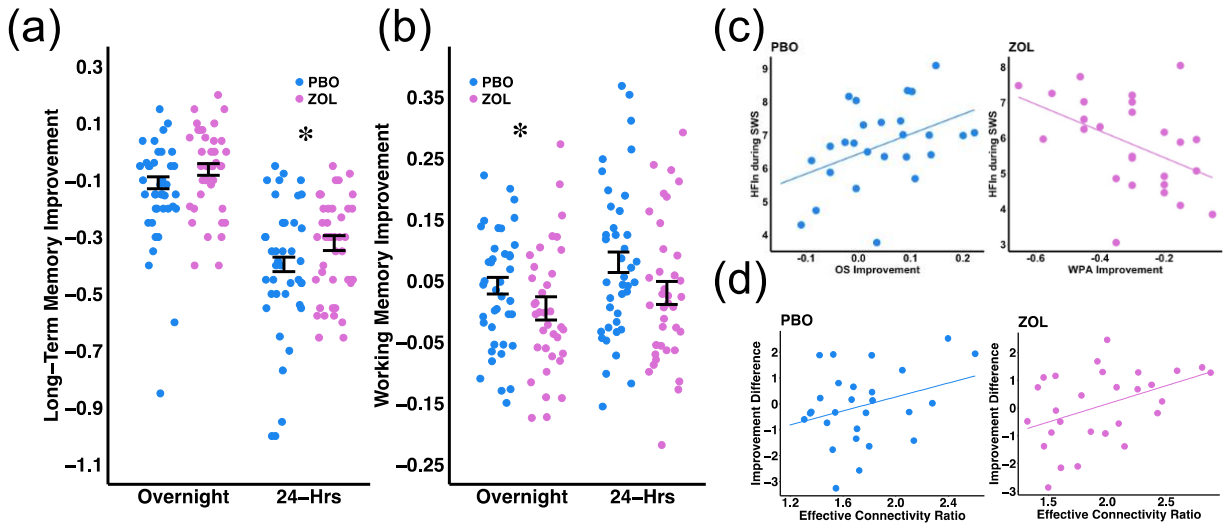


Figure 4.4 Zolpidem increases LTM but decreases WM improvement

(a) Long-term memory (WPA task) improvement by drug conditions and time. (Y axis: WPA Overnight [Test3-Test2] and 24-hr [Test3-Test1] improvement; asterisks indicate significant differences in behavioral changes between two drug conditions; *p<0.05) ZOL yielded greater but not significant overnight retention of WPA than the PBO condition (estimate= -0.1156, CI= (-0.2408, -0.0095), t= -1.8104, p= 0.0810), accounting for visit, as well as greater 24-hr retention of WPA than PBO visits (estimate= -0.1810, CI= (-0.3519, -0.0096), t= -2.0704, p= 0.0474), accounting for visit.

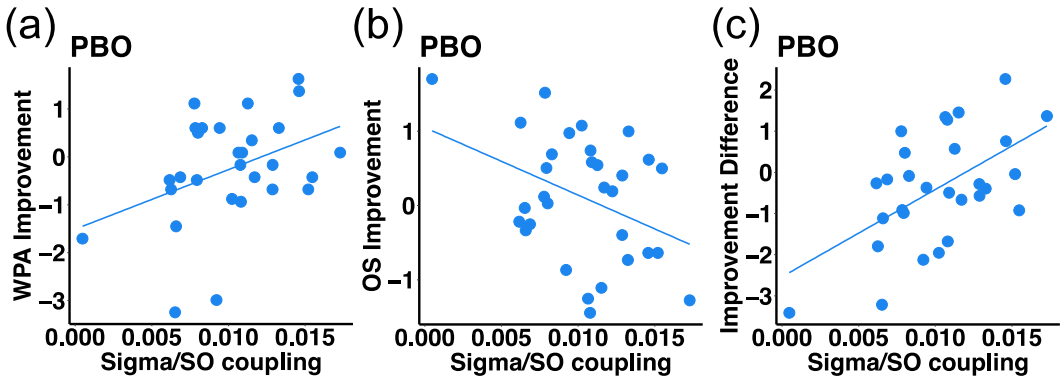
(b) Working memory (OS task) improvement by drug conditions and time. (Y axis: OS Overnight [Test3-Test2] and 24-hr [Test3-Test1] improvement; asterisks indicate significant differences in behavioral changes between two drug conditions; *p<0.05) PBO showed significantly greater overnight improvement of OS than ZOL visits (estimate= 0.1242, CI= (0.0201, 0.2284), t= 2.3377, p= 0.0260), accounting for Test 2 performance and visit, as well as greater but not significant 24-hr improvement of OS than ZOL visits (estimate=0.1000, CI= (-0.0184, 0.2185), t= 1.6546, p= 0.1081), accounting for Test 1 performance and visit.

(c) Functional role of vagal activity on memory. (Y axis: HFln during SWS, X axis: OS overnight and WPA 24-hr improvement) Vagal activity during SWS positively predicted working memory (OS task) improvement (r = .422; p = .032) but negatively predicted long-term memory (WPA task) improvement (r = -.460; p = .018). The difference between these two correlations was significant (Z = 3.67; p = .0001).

(d) Functional role of effective connectivity ratio on memory trade-off. (Y axis: normalized WPA improvement - normalized OS improvement score, X axis: effective connectivity ratio = HFInflow/ HFOutflow) Effective connectivity ratio (a higher ratio indicates a greater causal effect from sigma to vagal) during sleep positively predicted memory trade-off (a greater difference indicates a greater improvement in the WPA task than the OS task) during the zolpidem night (r = .429; p = .020), but not the placebo night (r = .251; p = .190). The difference between these two correlations not significant (Z = 0.78; p = 0.2177).

We, then, asked whether central and autonomic antagonism impacted the trade-off between LTM and WM improvement by correlating the effective connectivity ratio with the normalized LTM-WM difference score, where higher numbers represent greater LTM than WM improvement. We found a positive correlation between the effective connectivity ratio and normalized LTM-WM difference score in the zolpidem ($r = .429$; $p = .020$; Figure 4.4d right panel) and non-significant positive correlation in the placebo condition ($r = .251$; $p = .190$; Figure 4.4d left panel). These results suggested that the more central activity exerted influence on autonomic vagal activity, the more sleep was biased towards sigma-dependent LTM consolidation (and away from vagal-dependent WM processing). We further compared correlations between LTM-WM difference score and the effective connectivity ratio in the placebo versus zolpidem condition. The difference was not significant ($Z = 0.78$; $p = 0.2177$), suggesting that zolpidem amplified the natural vagal suppression by sigma and thus increased the magnitude of the correlations.

Figure 4.5 Functional roles of sigma power coupled with SO up-state on LTM and WM



(a) Long-term memory (WPA task) improvement positively correlated with sigma power coupled with SO up-state. (Y axis: normalized score of WPA 24-hr improvement; X axis: normalized sigma power coupled during the up-state of SOs; $r = .400$; $p = .034$)

(b) Working memory (OS task) improvement negatively correlated with sigma power coupled with SO up-state. (Y axis: normalized score of OS overnight improvement; X axis: normalized sigma power coupled during the up-state of SOs; $r = -.380$; $p = .033$)

(C) Improvement difference positively correlated with sigma power coupled with SO up-state. (Y axis: normalized WPA improvement - normalized OS improvement score; X axis: normalized sigma power coupled during the up-state of SOs; $r = .560$; $p = .002$)

Given the critical role for system consolidation of nested oscillations between sigma and SOs, the current findings led us to the prediction that greater sigma-SO coupling would evince increased LTM via suppressed WM. We tested this prediction by computing sigma power during the up-state of SOs and correlating this magnitude with the normalized LTM-WM improvement difference score (see Table 4.5 for SO counts and Sigma/SOs Summary Statistics; Table 4.6 for correlations). We found that zolpidem decreased the number of SOs, a finding consistent with prior literature that zolpidem shifts brain activity to faster frequencies. This decrease in SOs by zolpidem led us to examine coupling in the placebo condition, in which we found a significant positive correlation between sigma power during SOs up-state and difference in LTM-WM improvement (Figure 4.5), consistent with the notion that competitive dynamics underlie the fundamental mechanisms of cognitive improvements during sleep.

Discussion

The current work identified two neural mechanisms during NREM sleep that support the distinct enhancements in long-term and working memory. In experiment 1, we exploited the hypnotic zolpidem to enhance sigma activity during NREM sleep and report the novel finding that increasing sigma activity resulted in targeted vagal suppression during NREM. Next, we used the effective connectivity estimation technique to test the causal hypothesis that central sigma activity actively suppressed vagal autonomic activity. Consistent with our hypothesis, results showed that central sigma exerted greater causal control over autonomic vagal activity and that pharmacologically increasing sigma activity boosted causal information flow from central to autonomic channels and decreased flow from autonomic to central channels. In a separate set of subjects, we replicated the pharmacological intervention and tested the functional significance of the sigma-vagal mutual antagonism during NREM sleep by testing LTM and WM before and after a night of sleep. The physiological and effective connectivity results replicated those of experiment 1.

Moreover, the sigma-guided vagal suppression was associated with enhanced LTM retention at the cost of reduced WM improvement. Additionally, the magnitude of vagal suppression, as well as the degree of sigma-SO coupling, predicted a not previously reported trade-off between LTM and WM processing. These findings suggest evidence for a slow oscillation switch that toggles between separate and non-overlapping NREM mechanisms that support LTM and WM processing. Furthermore, this switch can be biased towards greater LTM consolidation by boosting sigma activity.

Sigma activity is proposed to facilitate plasticity by producing long-term changes in responsiveness in cortical neurons (Timofeev et al., 2002) and increasing dendritic Ca2+ influxes (Seibt et al., 2017), particularly enhanced when coupled to down-to-up transitions of the sleep slow oscillation. Recently, Dickey and colleagues demonstrated sigma activity may promote spike-timing-dependent plasticity (STDP), which facilitates long-term potentiation (LTP), the cellular mechanism thought to underlie learning and memory (Dickey et al., 2021). Thus, sigma activity may promote LTM via cellular synaptic plasticity. Furthermore, at the systems level, sigma nested within SOs may also support the replay of memory traces during consolidation (Latchoumane et al., 2017), and causally increasing sigma activity boosts hippocampal-dependent memory consolidation (Cairney et al., 2018; Mednick et al., 2013). The current findings demonstrate that sigma activity, especially when coupled with SOs also suppresses subcortical vagal activity with significant functional outcomes, specifically a reduction in WM.

Vagal influence on cognitive function is a core principle of the Neurovisceral Integration Model (Thayer & Lane, 2009a), which posits that ANS activity is a peripheral index of the integrity of prefrontal-autonomic networks that support inhibitory, goal-directed, high-order brain functions. The tenth cranial vagus nerve communicates peripheral information to and from the brainstem, with afferents projecting to higher-order, cognitive areas such as prefrontal cortex,

anterior cingulate, and amygdala. Additionally, descending projections from the PFC to the brainstem and hypothalamic structures allow for bi-directional communication between the central nervous system and the ANS through the vagus nerve. As such, high levels of vagally-mediated HRV are associated with superior executive function (Williams et al., 2019), working memory (Mosley et al., 2018), and emotional regulation (Mather & Thayer, 2018). Cognitive training including working memory has demonstrated that vagal activity reflects enhanced cognitive control of prefrontal networks (Lin, L Heffner, et al., 2017). Although sleep is not typically measured across the cognitive training interventions, the current findings suggest that executive function improvement may be mediated by the strengthening of prefrontal-autonomic networks during sleep.

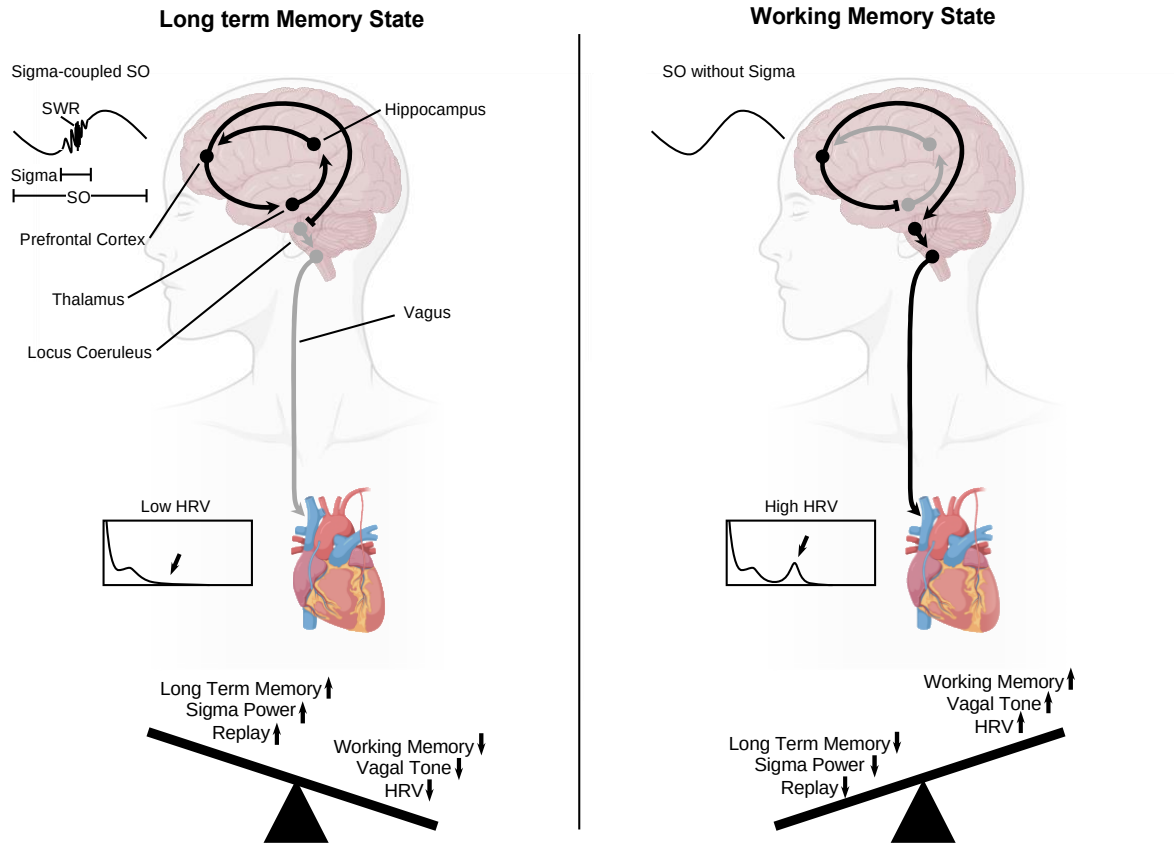
Parasympathetic vagal activity is highest during SWS compared to all other states of consciousness (Whitehurst et al., 2020). Vagal activity is strongly coupled with delta activity (< 4Hz) during SWS and vagal enhancement precedes the onset of SWS (Rothenberger et al., 2015). Several studies have linked SOs with WM improvement. For example, studies have shown that fronto-parietal SOs, but not sigma, predicts WM improvement (Ferrarelli et al., 2019; Pugin et al., 2015). However, not all studies report a consistent association between SOs and WM (Chen, Whitehurst, Naji, et al., 2020b; Lau et al., 2015b; MacDonald et al., 2018), and few accounts for autonomic activity. Chen and colleagues reported that vagal activity during SWS was a better predictor of WM improvement than SWA or vagal activity during wake (Chen, Whitehurst, Naji, et al., 2020a). In the current work, we found that changes in vagal autonomic activity during SWS, but not SOs per se, was critical for WM performance improvement. This, together with prior findings, suggests a non-negligible role of vagal influence on WM plasticity.

Given that both LTM and WM appear to rely on NREM sleep, one clear question emerges: How are the limited resources of NREM sleep shared across cognitive processes? The current findings are consistent with the hypothesis that competitive neural dynamics during NREM sleep

underlie cognitive improvement. Supporting this hypothesis, prior research has shown that vagal nerve stimulation activates neurons in the locus coeruleus (LC) and increases NE levels in the brain (Hassert et al., 2004; Roosevelt et al., 2006), and inactivation of LC impairs WM acquisition, while having no effect on consolidation or retention of spatial memories (Beste et al., 2016; Chamberlain et al., 2006; Khakpour-Taleghani et al., 2009; Pihlaja et al., 2020; Sun et al., 2017), whereas upregulating GABAergic networks impaired WM performance (Lozano-Soldevilla et al., 2014). On the other hand, using ripple-triggered fMRI in monkeys, Logothetis and colleagues demonstrated that ripples orchestrate a privileged state of enhanced central brain activity by silencing output from the diencephalon, midbrain and brainstem, regions associated with autonomic regulation, which may serve to boost communication between hippocampus and cortex (Logothetis et al., 2012). In addition, in both humans and mice, Lecci et al. (2017) demonstrated that heart rate and sigma power oscillate in antiphase with each other at 0.02 Hz, suggesting a periodic switch between sigma and autonomic activation every 50 seconds (Lecci et al., 2017).

Here, using effective connectivity, we demonstrated that a GABAergic agonist enhanced naturally occurring cortical sigma dominance over vagal autonomic activity. Similar vagolytic findings have been shown with zolpidem in persistent vegetative state patients (Machado et al., 2014, 2011). Furthermore, the magnitude of this central sigma influence on vagal activity predicted the trade-off between overnight LTM and WM improvement. Together with the previous literature, these finding suggest that sigma-dependent processes, including GABAergic hippocampal-thalamocortical networks, and vagal-dependent processes, including noradrenergic frontal-autonomic networks, may compete for sleep resources during NREM sleep. We hypothesize that the shared resource may be the SOs, which when coupled with ripple-nested sigma, promotes LTM and suppresses other processes, and when uncoupled, facilitates WM by enhancing prefrontal-autonomic networks. We further hypothesize that sigma may act as a gating mechanism that regulates SO resources for other processes, which would explain the mixed findings of SOs for WM

improvement. Given that approximately 20% of slow oscillations during NREM are sigma-coupled (Malerba et al., 2018), this leaves plenty of resources to be divided amongst other processes, including WM.



	Long Term memory	Working memory
Brain Regions	Thalamus, Hippocampus, Prefrontal cortex	Prefrontal cortex, Locus Coeruleus
Neuromodulators	GABA	Norepinephrine
Sleep Mechanisms	Coupling between Sharp Wave Ripple (SWR)-Sigma-Slow Oscillations (SO) reflects LTM systems consolidation.	Uncoupled SO during SWS reflects Prefrontal Cortex inhibitory network activation and greater autonomic vagal HRV.

Figure 4.6 Slow Oscillation Switch (SOS) Model

The model represents the proposed brain regions, primary neuromodulators, and sleep mechanisms involved in the Long-term memory state and the Working memory state that toggle throughout non-rapid eye movement (NREM) sleep. During the Long-Term Memory state, consolidation occurs via sigma-coupled SOs, which leads to reduced autonomic vagal-dependent activity and less WM improvement. During the Working Memory state, greater efficiency occurs during uncoupled SOs associated with increased autonomic vagal-dependent activity, which leads to reduced central sigma-dependent activity and less LTM consolidation.

These data suggest a trade-off in which the two memory processes (LTM and WM) alternate during NREM sleep via a complex interaction at the synaptic (GABA vs NE activation), systems (thalamocortical vs frontal-midbrain), and mechanistic level (sigma-coupled SO vs uncoupled SO) (see graphical model in Figure 4.6). Further research enhancing vagal activity and suppressing sigma activity is needed to show a double dissociation and tease apart these competitive mechanisms. Future work is also required to test the generalizability across multiple cognitive domains (i.e. motor learning) and tasks (i.e. non-associative LTM and N-back WM tasks) that relies on NREM sleep. The slow oscillation switch mechanism and separable sleep features associated with WM and LTM processing suggest directions for future translational research on cognitive disturbances observed in neurodegenerative disorders such as Alzheimer's and Parkinson's disease, both of which involve the decline of sleep.

Limitations and future research

Limitations of this study include using a convenience sample of both men and women, and a lack of hormonal status among the young women, which can have an impact on cardiac vagal activity (Schmalenberger et al., 2019) and sigma activity (de Zambotti et al., 2015). Future studies examining hormonal fluctuation are needed to understand the interaction between central sigma and ANS profiles during sleep and their impact on cognition. Additionally, though we did not measure respiration directly, we did analyze the frequency peak of HF (HFfp) in order to control for respiratory rate, which can affect the HRV. HFfp showed no difference between the two drug conditions and varied within a narrow range in the HF spectrum, between 0.22 and 0.26 Hz. Thus, it is unlikely that respiratory activity played a key role in zolpidem's modulation on HRV and memory. However, we cannot completely exclude the effect of drug on cardiopulmonary coupling, as may be detected using measures of coherence. In addition, our experimental design did not

include an adaptation night, and thus may have caused the “first-night effect”. However, the visits were counterbalanced by drug conditions, therefore the first-night effect should have canceled out across subjects. Furthermore, given that zolpidem is commonly prescribed to insomniacs, studies are needed to investigate if chronic use of zolpidem leads to WM deficits or biased memory trade-off during sleep. Lastly, due to methodological differences between EEG and ECG analyses, we measured sigma power as a proxy of spindles, which was not directly correlated with sleep-dependent behavioral changes. In addition, our study was limited by adhering to standard measures of vagal activity that require 5 min epochs, which reduced temporal specificity. This limitation constrains our effective connectivity analysis to all sleep epochs. It’s therefore crucial that future research develop validated markers of vagal activity in shorter windows. Our results are lack of temporal specificity of sleep micro events and thus future research with a greater temporal precision around physiological events is needed to provide insight into shifts between central- and autonomic-dependent activities.

Concluding Remarks

Here, I present a novel investigation into the interaction between autonomic and central nervous system during sleep. I presented three experimental studies, the first which examined the role of autonomic activities during sleep on WM improvement. From this study, we can glean two main points, 1) vagal/parasympathetic activity is boosted during NREM sleep in a nap, compared with wake or REM sleep, and 2) natural boost in vagal/parasympathetic activity during SWS may benefit gains in prefrontal inhibitory function in young adults. In the second experimental study, I examined autonomic-central coupling events during sleep and their impacts on WM improvement. In this study, I showed that 1) slow oscillations and spindles are boosted prior to the peak of the heart rate busts followed by a vagal surge, and that 2) slow oscillations coordinate with autonomic events during SWS to support sleep-dependent WM improvement.

In the third study, I used a pharmacological within-subjects, double-blind, placebo-controlled approach to identify separate and competing underlying mechanisms between autonomic and central activities supporting WM and LTM. WM is the ability to hold a small amount of information active and relevant for a short amount of time, whereas episodic LTM is a seemingly unlimited bank of autobiographical experiences, each of which can be explicitly evoked. Sleep, specifically brain activity during NREM sleep, has been shown to influence both types of memory processes. Additionally, vagal activity measured by HF-HRV is associated with WM, while studies investigating the effect of ANS on episodic memory yield inconsistent results. Therefore, the mechanism underlying how CNS and ANS activity during sleep coordinate to facilitate both types of cognitive processes is unknown. In this study, I showed that zolpidem, a GABA agonist, can increase central spindle activity while suppressing autonomic vagal activity, resulting in an increased LTM retention and a decreased WM improvement across the night. I further showed that the more spindles inhibiting vagal activity, the more sleep dependent LTM than WM benefit one

demonstrated. Based on these findings, I proposed that the brain switches between separate and non-overlapping mechanisms that support LTM and WM processing, and that the shared resource for which they compete may indeed be SOs. In this way, when coupled with ripple-nested spindles, SOs promote LTM and suppress other processes, and when uncoupled, facilitate WM by enhancing prefrontal-autonomic networks. The competitive dynamics between these networks are theoretically guided by animal studies showing antagonistic relations between brain regions that regulate autonomic activity versus memory replay (Logothetis et al., 2012; Novitskaya et al., 2016), and evidence for a periodic switch between spindles and autonomic activity (Lecci et al., 2017).

One might wonder what determines the priority of the switch mechanism if sleep acts like a switch that toggles between the LC-NE prefrontal-subcortical autonomic processes and the GABAergic thalamocortical-hippocampal replay? Here, I present two possibilities – a natural periodic switch versus an experience-dependent bias. Lecci et al. (2017) demonstrated a periodic alternating pattern between spindle bursts and heart rate accelerations, occurring every 50 seconds, supporting a possibility that the slow oscillation switch mechanisms alternate periodically under tonic conditions. Alternatively, learning, emotional experiences, novelty, or cognitive load, might determine prioritization. Consistent with this idea, more demanding memory tasks show a greater number of spindles during subsequent sleep (Gais et al., 2002). Similarly, intensive WM training can increase frontal SOs and vagal activity to a higher degree, compared to less-intense WM training (Lin, L Heffner, et al., 2017; Pugin et al., 2015). Futures studies investigating how our brain and body coordinate to control this slow oscillation switch would allow further understanding of the competitive dynamics between different memory domains.

Furthermore, although WM training studies have demonstrated that executive function in general and WM specifically does improve (Melby-Lervåg & Hulme, 2013) and recent studies show that sleep supports this improvement (Chen, Whitehurst, Naji, et al., 2020a; Zinke et al., 2018a), the

underlying mechanisms of this benefit, however, are unclear. We know little about how prefrontal-subcortical autonomic networks might coordinate SOs and vagal activity to facilitate WM. One study suggested an association between cognitive control, vagal activity, and automaticity in the prefrontal-subcortical autonomic networks. Lin and colleagues (2017) showed that cognitive training decreased functional connectivity in the bilateral striatum-prefrontal networks while increasing vagal activity, thereby facilitating performance in trained and untrained tasks, with fewer resources needed for successful cognitive inhibitory control (Lin, L Heffner, et al., 2017). However, how such dynamics are modulated during sleep or SOs remains unexplored. Future neural imaging studies with simultaneous EEG-fMRI are crucial to allow understanding of the neural mechanisms underlying WM plasticity during specific sleep events.

Taken together, even though significant progress has been made over the past decade, there is still much to understand about the role of sleep in different cognitive domains. In my dissertation work, I present several lines of research on the role of heart-brain interaction during sleep in sleep-dependent cognitive gains. My works collectively demonstrate a scenario in which episodic LTM and WM are supported by separate circuitry that vie for limited resources during sleep. Importantly, I highlight the potential that SOs could be further divided into sub-categories implicated in different functions, as electrophysiological events that share the same frequency may have separate functions, a possibility recently explored by Ngo and colleagues (2019), showing a functional dissociation between delta and SOs, with delta waves facilitating forgetting whereas SOs are more likely to couple with spindles and facilitating episodic LTM consolidation (Kim et al., 2019; Ngo et al., 2019). Identifying autonomic-central biomarkers during sleep for different cognitive processes and understanding their competitive dynamics may facilitate novel insights to the memory models in the field and provide new targets to combat neurodegenerative disease.

Table 2.1. Summary of HRV Parameters Across Sleep Stages

Stage	Wake	Stage 2	SWS	REM	
RR (ms)	949.46	1006.61	1001.21	923.71	***
	(21.76)	(25.51)	(30.73)	(40.28)	
RMSSD	4.24	4.35	4.23	4.14	**
	(0.08)	(0.07)	(0.11)	(0.17)	
HF HRV	6.77	7.04	6.87	6.52	***
	(0.15)	(0.14)	(0.19)	(0.32)	
HFnu	52	59	71.8	46.6	***
	(2.3)	(2.5)	(2.7)	(3.5)	

Data are reported as Mean. Standard errors are shown in the rows below the Mean. Note: RR = RR intervals; RMSSD = Root mean square of successive differences; HF HRV= Power in the Low Frequency band of the HRV spectrum, often between 0.04 - 0.15 Hz; HFnu = HF/(HF+LF)%; N2 = Stage 2 Sleep; SWS = Slow Wave Sleep; REM = Rapid Eye Movement sleep. Asterisks indicate significant main effects of Sleep Stages on HRV indices (**$p < 0.01$; ***$p < 0.001$).

Table 2.2. Karolinska Sleepiness Scale (KSS) scores across the day

Session	Wake (N=51)	Nap (N=54)
Session 1	5.31 (0.29)	5.96 (0.28)
Session 2	4.98 (0.30)	3.35 (0.20)

Data are reported as Mean (Standard Error).

Table 3.1. Summary of Sleep Architecture

	(n=49)
TIB (min)	78.069 (3.1)
TST (min)	61.500 (2.94)
SOL (min)	7.664 (0.99)
Stage 1 (min)	4.586 (0.47)
Stage 2 (min)	31.448 (1.94)
SWS (min)	19.224 (1.96)
REM (min)	6.241 (1.09)
WASO (min)	6.560 (0.88)
SE (%)	77.588 (2.21)

*Note: Data are reported as Mean (standard error); TIB = Total Time in Bed; TST = Total Sleep Time; SWS = Slow Wave Sleep; REM = Rapid Eye Movement sleep; WASO = Wake After Sleep Onset (calculated as the minutes of wake after first epoch of sleep); SOL = Sleep Latency (calculated as the time to first epoch of sleep); SE = Sleep Efficiency (calculated as 100*TST/TIB). All stats are represented in minutes besides SE which is in percentage.*

Table 3.2. Summary of EEG Power Across Sleep Stages

Stage (N)	Stage 2 (49)	SWS (38)	REM (19)
SWA (0.5-1Hz)	70.8 (5.08)	165.7 (12.7)	85.4 (37.0)
Delta (0.5-4Hz)	135 (38.5)	302 (23.8)	166 (77)
Theta (4-8Hz)	10.7 (2.35)	14.0 (1.37)	13.7 (3.41)
Sigma (12-15Hz)	4.91 (1.08)	5.42 (0.493)	5.13 (1.47)

Data are reported as Mean (standard error).

Table 3.3. Summary of HR Burst Density (per Minute) Across Sleep Stages

Stage 2	SWS	REM	Wake
0.932 (0.0393)	0.896 (0.0443)	0.760 (0.0600)	0.358 (0.0432)

Data are reported as Mean (standard error). Note: SWS = Slow Wave Sleep; REM = Rapid Eye Movement sleep.

Table 3.4. Change Scores for ACE variables

Table 3.4a. Change Scores for ACE variables during SWS

Window			-10	-5	+5	+10
SWA	Frontal	Mean	-0.036	0.183***	0.047	0
		S.E.	0.024	0.034	0.030	0.030
	Central	Mean	-0.047	0.197***	0.047	0.022
		S.E.	0.017	0.019	0.018	0.017
Sigma	Frontal	Mean	-0.006	0.083***	0.014	-0.003
		S.E.	0.022	0.014	0.022	0.018
	Central	Mean	0.003	0.072***	0.015	-0.005
		S.E.	0.020	0.015	0.021	0.018
RR_{HF}		Mean	0.022	0.076*	0.138***	0.045
		S.E.	0.016	0.022	0.022	0.022

Asterisks show the significant differences (*p<.05;***p<.001) between a change score in a bin and zero (baseline), adjusted by Bonferroni correction.

Table 3.4b. Change Scores for ACE variables during Stage 2 Sleep

Window			-10	-5	+5	+10
SWA	Frontal	Mean	-0.036	0.147***	-0.026	-0.047
		S.E.	0.011	0.019	0.011	0.009
	Central	Mean	-0.034	0.132***	-0.023	-0.040
		S.E.	0.010	0.016	0.010	0.009
Sigma	Frontal	Mean	-0.008	0.137***	-0.008	-0.098
		S.E.	0.017	0.020	0.016	0.019
	Central	Mean	-0.011	0.117***	-0.020	-0.104
		S.E.	0.016	0.017	0.015	0.019
RR_{HF}		Mean	0.006	0.062**	0.179***	0.029
		S.E.	0.009	0.014	0.014	0.010

Asterisks show the significant differences (**p<.01; ***p<.001) between a change score in a bin and zero (baseline), adjusted by Bonferroni correction.

Table 3.5. Regression models: *ACE predicting WM improvement*

Table 3.5a. Regression models: ACE frontal channels predicting WM improvement

Variables	Model 1			Model 2 (PrePost)			Model 2 (PreBase)		
	Estimate	Std. Error	t-value	Estimate	Std. Error	t-value	Estimate	Std. Error	t-value
WM baseline	-0.266	0.087	-3.072**	-0.178	0.087	-2.060*	-0.215	0.089	-2.397*
Overall SWA	<0.001	<0.001	-1.019	<0.001	<0.001	-1.220	<0.001	< 0.001	-0.780
ACE SWA				0.012	0.004	2.550*	0.021	0.126	1.666
F			4.798			5.974			4.319
R^2			0.248			0.390			0.316
Adjusted R^2			0.196			0.325			0.243
Change in adj R^2						0.188*			0.068

†p < .1, *p < .05, **p<.01, ***p<.001

Table 3.5b. Regression models: ACE central channels predicting WM improvement

Variables	Model 1			Model 2 (PrePost)			Model 2 (PreBase)		
	Estimate	Std. Error	t-value	Estimate	Std. Error	t-value	Estimate	Std. Error	t-value
WM baseline	-0.257	0.085	-3.011**	-0.204	0.087	-2.352*	-0.192	.085	-2.247*
Overall SWA	<.001	<.001	-1.017	<.001	<.001	-1.275	<.001	< .001	-0.854
ACE SWA				.008	.004	1.847†	.316	.144	2.194*
F			4.796			4.6			5.222
R^2			0.248			0.330			.359
Adjusted R^2			0.196			0.258			0.290
Change in adj R^2						0.082†			0.110*

†p < .1, *p < .05, **p<.01, ***p<.001

Table 4.1. Descriptive statistics for Demographics

	Experiment 1	Experiment 2
Age (years)	20.38 (1.88)	20.85 (2.97)
Male/female	17/17 (50/50)	19/19 (50/50)
Education (years)	14.13 (1.66)	14.67 (2.17)
ESS	7.59 (2.81)	6.61 (2.42)
BMI (kg/m^2)	24.29 (3.73)	24.82 (3.45)
Weight (lb)	152.38 (31.39)	158.84 (28.17)
Right-handed/ left-	34/0 (100/0)	35/3 (92/8)

Note: Data are reported as Mean (standard deviation) for quantitative variables and N (%) for categorical variables; ESS: Epworth Sleepiness Scale; BMI: Body Mass Index.

Table 4.2. Sleep Architecture

Table 4.2a. Experiment 1 Sleep Architecture

Drug	PBO	ZOL	
TIB (min)	531.1983 (10.0147)	512.7203 (9.9295)	*n.s.*
TST (min)	471.5086 (11.0225)	470.7034 (10.9287)	*n.s.*
Stage 1	15.0372 (1.8978)	10.7450 (1.8899)	*n.s.*
Stage 2	244.0504 (8.7200)	234.4514 (8.7642)	*n.s.*
SWS (min)	95.2869 (6.1151)	114.6660 (6.1580)	***
REM (min)	115.2036 (5.8510)	106.0416 (5.8623)	*n.s.*
WASO	37.3222 (5.7574)	26.4467 (5.7965)	*
SE (%)	87.6834 (2.1189)	89.7306 (2.1284)	*n.s.*

*Note: Data are reported as Mean (standard error). TIB = Time in bed; TST = Total Sleep Time; WASO = Wake After Sleep Onset (calculated as the minutes of wake after first epoch of sleep); SE = Sleep Efficiency (calculated as 100*TST/Total Time in Bed). Asterisks indicate significant differences between conditions (n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001).*

Table 4.2b. Experiment 2 Sleep Architecture

Drug	PBO	ZOL	
TIB (min)	582.2941 (6.2418)	575.8939 (5.4352)	*n.s.*
TST (min)	541.1471 (7.8834)	538.4394 (7.5856)	*n.s.*
Stage 1	13.4706 (1.4540)	11.8485 (1.9770)	*n.s.*
Stage 2	285.6176 (8.3986)	284.5909 (7.6952)	*n.s.*
SWS (min)	109.3676 (6.1462)	125.4091 (7.3790)	**
REM (min)	132.4412 (5.9244)	116.197 (5.6641)	**
WASO	29.5735 (4.6177)	24.2576 (4.2369)	*n.s.*
SE (%)	92.9503 (0.9376)	93.4436 (0.8178)	*n.s.*

*Note: Data are reported as Mean (standard error). TIB = Time in bed; TST = Total Sleep Time; WASO = Wake After Sleep Onset (calculated as the minutes of wake after first epoch of sleep); SE = Sleep Efficiency (calculated as 100*TST/Total Time in Bed). Asterisks indicate significant differences between conditions (n.s. p >0.0; *p < 0.05; **p < 0.01; ***p < 0.001).*

Table 4.3. Summary of HRV Parameters Across Sleep Stages

Table 4.3a. Experiment 1 Summary of HRV Parameters Across Sleep Stages

Stage	Rest			Stage 2			SWS			REM		
Drug/N	PBO/48	ZOL/45		PBO/54	ZOL/54		PBO/52	ZOL/53		PBO/50	ZOL/54	
Epochs	0.9265 (1.0750)	0.7516 (1.1060)	n.s.	28.3514 (1.0469)	29.4467 (1.0195)	n.s.	12.8394 (1.0381)	16.7343 (1.0278)	**	17.1589 (1.0560)	14.3541 (1.0195)	*
RR (ms)	943.8518 (20.0360)	939.4200 (20.1655)	n.s.	1019.4037 (19.9060)	982.7458 (19.7599)	**	1002.7592 (19.8653)	922.0266 (19.7976)	***	975.6168 (19.9479)	970.5194 (19.7599)	n.s.
RMSSD (ln)	4.2359 (0.0733)	4.2642 (0.0739)	n.s.	4.2683 (0.0727)	4.2194 (0.0719)	n.s.	4.1433 (0.0725)	3.9617 (0.0722)	***	4.3145 (0.0729)	4.3611 (0.0719)	n.s.
HF (ln ms²)	6.6928 (0.1443)	6.7489 (0.1455)	n.s.	6.8488 (0.1431)	6.7663 (0.1418)	n.s.	6.5898 (0.1427)	6.2717 (0.1422)	**	6.8766 (0.1435)	6.9565 (0.1418)	n.s.
LF (ln ms²)	6.4687 (0.1066)	6.6036 (0.1088)	n.s.	6.6530 (0.1045)	6.5559 (0.1024)	n.s.	5.6299 (0.1039)	5.6921 (0.1030)	n.s.	6.9610 (0.1052)	6.9894 (0.1024)	n.s.
TP (ln ms²)	7.7537 (0.0993)	7.9607 (0.1009)	n.s.	7.9888 (0.0977)	7.9231 (0.0960)	n.s.	7.2827 (0.0972)	7.2369 (0.0964)	n.s.	8.3585 (0.0982)	8.4724 (0.0960)	n.s.
HF_{nu}	0.5479 (0.0222)	0.5279 (0.0225)	n.s.	0.5592 (0.0220)	0.5541 (0.0218)	n.s.	0.7044 (0.0219)	0.6194 (0.0218)	***	0.4774 (0.0221)	0.4856 (0.0218)	n.s.
HF_{pf}	0.2626 (0.0079)	0.2607 (0.0080)	n.s.	0.2506 (0.0078)	0.2592 (0.0077)	n.s.	0.2689 (0.0078)	0.2774 (0.0077)	n.s.	0.2276 (0.0078)	0.2502 (0.0077)	n.s.

*Data are reported as Mean (standard error). N: number of nights. Epochs: number of consecutive 5-min epochs per stage. Asterisks indicate significant differences between conditions (corrected by Tukey's; n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001)*

Table 4.3b. Experiment 2 Summary of HRV Parameters Across Sleep Stages (Q2 and Q3)

Stage	Stage 2			SWS			REM		
Drug/ N	PBO/36	ZOL/35		PBO/35	ZOL/33		PBO/36	ZOL/35	
Epochs	17.92 (0.864)	19.71 (0.876)	n.s.	5.28 (0.963)	4.50 (0.980)	n.s.	11.00 (0.876)	7.40 (0.876)	**
RR (ms)	1005 (24.8)	960 (24.8)	***	980 (25.8)	926 (26.0)	***	952 (24.9)	930 · (25.5)	n.s.
RMSSD (ln)	4.21 (.0999)	4.04 (.0999)	**	4.10 (.1058)	3.78 (.1065)	***	4.13 (.1003)	4.04 (.1021)	n.s.
HF (ln ms²)	6.81 (.187)	6.56 (.187)	*	6.56 (.200)	5.96 (.201)	***	6.56 (.188)	6.46 (.192)	n.s.
LF (ln ms²)	6.43 (.126)	6.30 (.126)	n.s.	5.61 (.138)	5.63 (.139)	n.s.	6.80 (.127)	6.66 (.131)	n.s.
TP (ln ms²)	7.84 (.125)	7.69 (.125)	n.s.	7.27 (.136)	6.97 (.137)	*	8.20 (.125)	8.13 (.129)	n.s.
HF_{nu}	.590 (.0245)	.562 (.0245)	n.s.	.692 (.0266)	.571 (.0269)	***	.444 (.0247)	.463 (.0253)	n.s.
HF_{pf}	0.242 (.00566)	0.242 (.00567)	n.s.	0.257 (.00647)	0.262 · (.00656)	n.s.	0.226 (.00572)	0.223 (.00597)	n.s.

*Data are reported as Mean (standard error). N: number of nights. Epochs: number of consecutive 5-min epochs per stage. Asterisks indicate significant differences between conditions (corrected by Tukey's; n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001)*

Table 4.3c. Experiment 2 Summary of HRV Parameters Across Sleep Stages (Whole Night)

Stage	Rest			Stage 2			SWS			REM		
Drug	PBO/36	ZOL/35		PBO/36	ZOL/35		PBO/35	ZOL/33		PBO/36	ZOL/35	
Epochs	1.1952 (1.3512)	1.2298 (1.3513)	n.s.	32.2223 (1.1923)	34.0776 (1.2092)	n.s.	14.9445 (1.1923)	17.5057 (1.2267)	n.s.	17.5834 (1.1923)	12.9634 (1.2092)	**
RR (ms)	921.3591 (25.5762)	916.2846 (25.5832)	n.s.	995.8569 (24.7979)	965.1472 (24.8780)	*	960.8052 (24.7979)	912.5708 (24.9602)	**	952.8750 (24.7979)	946.8405 (24.8780)	n.s.
RMSSD (ln)	4.1161 (0.1033)	4.0245 (0.1033)	n.s.	4.2109 (0.0999)	4.1360 (0.1002)	n.s.	4.0433 (0.0999)	3.8658 (0.1006)	**	4.1640 (0.0999)	4.2163 (0.1002)	n.s.
HF (ln ms^2)	6.5489 (0.1914)	6.4349 (0.1915)	n.s.	6.8411 (0.1844)	6.8331 (0.1851)	n.s.	6.5257 (0.1844)	6.2111 (0.1859)	*	6.6926 (0.1844)	6.8286 (0.1851)	n.s.
LF (ln ms^2)	6.3585 (0.1601)	6.1928 (0.1602)	n.s.	6.5391 (0.1499)	6.6276 (0.1510)	n.s.	5.5960 (0.1499)	5.6329 (0.1520)	n.s.	6.8107 (0.1499)	6.9788 (0.1510)	n.s.
TP (ln ms^2)	7.6236 (0.1964)	7.5546 (0.1965)	n.s.	7.9143 (0.1817)	8.1351 (0.1832)	n.s.	7.2577 (0.1817)	7.1264 (0.1848)	n.s.	8.2623 (0.1817)	8.5266 (0.1832)	n.s.
HF_{nu}	0.5366 (0.0257)	0.5547 (0.0257)	n.s.	0.5696 (0.0239)	0.5661 (0.0241)	n.s.	0.6875 (0.0239)	0.6143 (0.0243)	**	0.4654 (0.0239)	0.4694 (0.0241)	n.s.
HF_{pf}	0.2655 (0.0082)	0.2477 (0.0082)	n.s.	0.2396 (0.0074)	0.2397 (0.0074)	n.s.	0.2596 (0.0074)	0.2625 (0.0075)	n.s.	0.2219 (0.0074)	0.2257 (0.0074)	n.s.

*Data are reported as Mean (standard error). Epochs: number of consecutive 5-min epochs per stage. Asterisks indicate significant differences between conditions (corrected by Tukey's; n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001)*

Table 4.4. Normalized EEG Power during NREM Modulated by Drug Conditions

Table 4.4a. Experiment 1 Normalized EEG Power during NREM Modulated by Drug Conditions (Whole Night)

Stage		Stage 2			SWS		
Drug		PBO	ZOL		PBO	ZOL	
SWA	Frontal	.2938 (.0161)	.3063 (.0169)	n.s.	.4436 (.0209)	.4637 (.0200)	n.s.
0.5-2Hz	Central	.2668 (.0142)	.2821 (.0162)	n.s.	.4104 (.0201)	.4409 (.0203)	n.s.
	Parietal	.2539 (.0139)	.2647 (.0159)	n.s.	.3968 (.0206)	.4286 (.0214)	n.s.
	Occipital	.2212 (.0138)	.2387 (.0158)	n.s.	.3437 (.0212)	.3887 (.0225)	n.s.
Delta	Frontal	.1966 (.0135)	.1952 (.0137)	n.s.	.2550 (.0150)	.2329 (.0131)	n.s.
1-4Hz	Central	.1895 (.0128)	.1900 (.0135)	n.s.	.2294 (.0145)	.2159 (.0131)	n.s.
	Parietal	.1832 (.0123)	.1807 (.0127)	n.s.	.2163 (.0142)	.2014 (.0127)	n.s.
	Occipital	.1651 (.0120)	.1723 (.0124)	n.s.	.1806 (.0134)	.1812 (.0119)	n.s.
Sigma	Frontal	.0123 (.0017)	.0149 (.0013)	n.s.	.0059 (.0015)	.0059 (.0005)	n.s.
12-16Hz	Central	.0166 (.0018)	.0212 (.0018)	*	.0073 (.0016)	.0078 (.0006)	n.s.
	Parietal	.0223 (.0022)	.0274 (.0022)	*	.0088 (.0016)	.0095 (.0008)	n.s.
	Occipital	.0180 (.0019)	.0223 (.0019)	*	.0076 (.0016)	.0079 (.0007)	n.s.
Theta	Frontal	.0439 (.0045)	.0370 (.0029)	n.s.	.0327 (.0037)	.0241 (.0014)	n.s.
4-8Hz	Central	.0518 (.0048)	.0432 (.0032)	n.s.	.0344 (.0038)	.0256 (.0015)	n.s.
	Parietal	.0580 (.0049)	.0477 (.0035)	n.s.	.0368 (.0039)	.0275 (.0018)	n.s.
	Occipital	.0664 (.0058)	.0587 (.0044)	n.s.	.0432 (.0042)	.0360 (.0026)	n.s.

*Data are reported as Mean (standard error). Powers were averaged bilaterally from channel F3, F4, C3, C4, P3, P4, O1, O2. (Asterisks indicate significant differences between drug conditions by linear-mixed models; n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001).*

Table 4.4b. Experiment 2 Normalized EEG Power during NREM Modulated by Drug Conditions (Q2 & Q3)

Stage		Stage 2			SWS		
Drug		PBO	ZOL		PBO	ZOL	
SWA	Frontal	.4683 (.0107)	.4723 (.0133)	n.s.	.6254 (.0148)	.6188 (.0181)	n.s.
0.5-2Hz	Central	.4216 (.0109)	.4271 (.0131)	n.s.	.5898 (.0134)	.5849 (.0178)	n.s.
	Parietal	.4039 (.0098)	.4030 (.0129)	n.s.	.5888 (.0138)	.5746 (.0187)	n.s.
	Occipital	.3602 (.0113)	.3660 (.0142)	n.s.	.5199 (.0167)	.5087 (.0223)	n.s.
Delta	Frontal	.3117 (.0103)	.3041 (.0113)	n.s.	.3501 (.0114)	.3057 (.0125)	**
1-4Hz	Central	.2970 (.0099)	.2958 (.0106)	n.s.	.3210 (.0108)	.2829 (.0126)	**
	Parietal	.2898 (.0091)	.2870 (.0106)	n.s.	.3158 (.0092)	.2740 (.0126)	**
	Occipital	.2735 (.0114)	.2772 (.0121)	n.s.	.2863 (.0104)	.2531 (.0132)	*
Sigma	Frontal	.0238 (.0019)	.0286 (.0026)	**	.0096 (.0010)	.0121 (.0015)	*
12-16Hz	Central	.0314 (.0023)	.0394 (.0031)	***	.0125 (.0011)	.0161 (.0018)	*
	Parietal	.0395 (.0030)	.0497 (.0039)	***	.0150 (.0014)	.0197 (.0022)	*
	Occipital	.0330 (.0022)	.0401 (.0031)	**	.0130 (.0012)	.0164 (.0018)	n.s.
Theta	Frontal	.0693 (.0037)	.0605 (.0037)	***	.0436 (.0026)	.0353 (.0025)	**
4-8Hz	Central	.0816 (.0041)	.0724 (.0040)	**	.0492 (.0031)	.0402 (.0030)	**
	Parietal	.0897 (.0043)	.0785 (.0042)	**	.0548 (.0035)	.0443 (.0034)	**
	Occipital	.1046 (.0056)	.0944 (.0056)	n.s.	.0703 (.0049)	.0585 (.0051)	*

*Data are reported as Mean (standard error). Powers were averaged bilaterally from channel F3, F4, C3, C4, P3, P4, O1, O2. (Asterisks indicate significant differences between drug conditions by paired t-tests; n.s. p >0.05; *p < 0.05; **p < 0.01; ***p < 0.001).*

Table 4.5. Correlations between HRV Parameters and Behavioral Improvements

	WPA						OS					
	HFln		RMSSDln		HFnu		HFln		RMSSDln		HFnu	
Drug	PBO	ZOL	PBO	ZOL	PBO	ZOL	PBO	ZOL	PBO	ZOL	PBO	ZOL
Stage 2	r = -.035 p = .851	r = -.460 p = .008	r = -.094 p = .615	r = -.508 p = .003	r = -.036 p = .846	r = -.406 p = .021	r = .051 p = .773	r = .015 p = .933	r = .086 p = .629	r = -.065 p = .709	r = -.019 p = .915	r = .117 p = .501
SWS)	r = -.096 p = .654	r = -.460 p = .018	r = -.168 p = .431	r = -.513 p = .007	r = -.014 p = .948	r = -.350 p = .080	r = .422 p = .032	r = .131 p = .507	r = .397 p = .044	r = .068 p = .731	r = .141 p = .491	r = .220 p = .360

Data are reported as Pearson's correlation coefficients (r) and p-values (p).

Table 4.6. SOs Counts and Sigma/SOs by Drug Conditions

Drug		PBO	ZOL	
SO	F3	169.242 (28.061)	160.909 (44.758)	n.s.
Counts	F4	185.242 (34.602)	174.484 (49.172)	n.s.
	C3	122.636 (20.164)	105.485 (25.098)	n.s.
	C4	102.970 (22.061)	94.333 (22.011)	n.s.
	P3	104.212 (18.445)	78.757 (16.317)	*
	P4	94.394 (18.007)	71.303 (16.093)	*
SO up-state	F3	0.01066241 (0.000572956)	0.01052726 (0.0007072569)	n.s.
Sigma	F4	0.01179984 (0.0009264091)	0.01172965 (0.0007314609)	n.s.
Normalized	C3	0.01175520 (0.0006375368)	0.01146652 (0.0007709227)	n.s.
Power	C4	0.01066014 (0.0007590402)	0.01076715 (0.0006134255)	n.s.
	P3	0.01034928 (0.0006057417)	0.01170495 (0.0008417385)	n.s.
	P4	0.010588097 (0.0006876312)	0.009728913 (0.0006714047)	n.s.

*Data are reported as Mean (standard error). (Asterisks indicate significant differences between drug conditions by paired t-tests; n.s. p >0.05; *p < 0.05).*

Table 4.7. Correlations between Sigma/SOs couplings and Behavioral Improvements

PBO	F3	F4	C3	C4	P3	P4
WPA	r = .33 p = .082	r = .28 p = .150	r = .24 p = .200	r = .34 p = .073	r = .40 p = .034	r = .21 p = .27
OS	r = -.51 p = .003	r = -.33 p = .075	r = -.31 p = .085	r = -.17 p = .370	r = -.38 p = .033	r = -.16 p = .400
WPA - OS	r = .59 p < .001	r = .45 p = .016	r = .39 p = .036	r = .38 p = .041	r = .560 p = .002	r = .29 p = .130

ZOL	F3	F4	C3	C4	P3	P4
WPA	r = .16 p = .378	r = -.11 p = .543	r = .16 p = .373	r = -.18 p = .351	r = .12 p = .530	r = -.09 p = .632
OS	r = .20 p = .291	r = -.04 p = .817	r = .11 p = .559	r = -.18 p = .351	r = .24 p = .217	r = -.14 p = .472
WPA - OS	r = -.10 p = .598	r = -.60 p = .758	r = -.02 p = .915	r = -.01 p = .950	r = -.12 p = .551	r = .02 p = .911

Data are reported as Pearson's correlation coefficients (r) and p-values (p).

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