

# Autonomic Activity during a Daytime Nap Facilitates Working Memory Improvement

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## 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 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 and Graham (1974), it comprises a verbal system and a visuospatial system, which are both controlled by a central executive. 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, Cowan, Bunting, Theriault, & Minkoff, 2002; Engle, Tuholski, Laughlin, & Conway, 1999). Decades of work have shown strong neural activity in pFC when performing WM tasks (Wager & Smith, 2003; Levy & Goldman-Rakic, 2000; Smith & Jonides, 1998; Fuster & Alexander, 1971). Considering the importance of WM for cognitive functions, the question of possibly modifying WM in the pursuit of boosting related cognitive functions has been raised. Scientific interest in cognitive interventions designed to maintain or improve cognitive functions has been rapidly increasing over the last decade.

WM training typically requires practice over a span of days, weeks, or months, suggesting that offline, sleep-dependent mechanisms may be involved 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 and procedural memories as well as maintaining executive function, including sustained attention and WM (Könen, Dirk, & Schmiedek, 2015; Vriend et al., 2013). Indeed, it is known that sleep deprivation/restriction detrimentally affects WM. For example, sleep deprivation/restriction can lead to impairment in sustained attention (Lo et al., 2012; Goel, Rao, Durmer, & Dinges, 2009) 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 neural 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, Ong, Leong, Gooley, & Chee, 2016; Lo et al., 2012), much less is known about the direct contribution of sleep-specific mechanisms supporting WM improvement. Recently, studies that directly tested the effect of posttraining sleep on WM performance suggested that a period of sleep, compared to wake, facilitates WM (Zinke, Noack, & Born, 2018; Lau, Wong, Lau, Hui, & Tseng, 2015; Kuriyama, Mishima, Suzuki, Aritake, & Uchiyama, 2008). 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., 2018; Kuriyama et al., 2008) or a nap (Lau et al., 2015), in comparison with daytime periods

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of wakefulness. One plausible neurophysiological mechanism for such training improvement is slow wave sleep (SWS). SWS has received increasing attention because of 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 (Dang-Vu et al., 2010; Takashima et al., 2006; Tononi & Cirelli, 2003). Intriguingly, several studies have shown a specific association between EEG activity during SWS in the enhancement of WM. Pugin et al. (2015) demonstrated a correlation between slow wave activity during SWS in frontal areas and WM performance after 3 weeks of WM training (Pugin et al., 2015). Furthermore, slow wave activity during SWS has been shown to predict WM gains across a period of sleep in both young (Ferrarelli et al., 2019) and older (Sattari, Whitehurst, Ahmadi, & Mednick, 2019) adults. 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 (see Whitehurst, Chen, Naji, & Mednick, 2020, for a review). Thayer and others have published a body of research implicating cardiac vagal influence on a range of cognitive abilities supported by the pFC (Smith et al., 2017; Thayer & Lane, 2009; Lane et al., 2001). Descending projections from pFC to the brainstem and hypothalamic structures allow for bidirectional communication between the central nervous system and the ANS through the vagus nerve (Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Packard et al., 1995), and thus prominent models of ANS and cognition, including the neurovisceral integration model (Smith et al., 2017; Thayer & Lane, 2009), have focused on the impact of vagal cardiac activity on executive functions. In humans, a well-established method to noninvasively examine autonomic activity is heart rate variability (HRV), which measures systematic variation in the beat-to-beat interval of the heart (Shaffer, McCraty, & Zerr, 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, Mosley, & Thayer, 2017; Shaffer et al., 2014). For frequency-domain analysis, spectral analysis of the cardiac signal in the high frequency (HF) range (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, Johnsen, & Thayer, 2003; operation-span task: Mosley, Laborde, & Kavanagh, 2018) and cognitive inhibition (i.e., Stroop task; Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004). In addition, reducing HRV, via aerobic detraining, comes at a 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 (Jacobs et al., 2015; Clark et al., 1999), 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 nonrapid eye movement (NREM) sleep (i.e., Stage 1, Stage 2, and SWS; Trinder et al., 2001). In addition, similar HRV profiles have been shown between daytime (naps) and nighttime sleep (Whitehurst, Naji, & Mednick, 2018; Cellini, Whitehurst, McDevitt, & Mednick, 2016). 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 the day (difference score between Test 2 and 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 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 rapid eye movement (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

One hundred four young adults (age: 18–23 years [ $M = 20.7$ ,  $SD = 2.95$ ], 60 men) 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. The personal health histories were measured twice. First, during a prescreening questionnaire in which a general health condition report was collected over the online survey, the eligibility was determined. Second, eligible participants were invited to participate in an orientation in which they were given details about the study and interviewed by a trained graduate student. Participants who met any of the following exclusion criteria were excluded from the study: (a) have extreme morning- or evening-type tendencies; (b) have a sleep disorder (reported or detected on the questionnaires); (c) have any personal or immediate family (i.e., first-degree relative) history of diagnosed significant psychopathology; (d) have a personal history of head injury with loss of consciousness greater than 2 min or seizures; (e) history of substance dependence; (f) current use of any psychotropic medications; (g) have any cardiac, respiratory, or other medical condition that may affect cerebral metabolism; and (h) have noncorrectable vision and auditory impairments. Participants who did not meet any of the exclusion criteria above and also met all the following inclusion criteria were enrolled in the study: (a) aged 18–39 years; (b) healthy, nonsmoking adult without major medical problems; (c) have completed at least 12 years of education; (d) have a regular sleep–wake schedule, defined as obtaining 6.5–9 hr of sleep per night, with a habitual bedtime between 10 p.m. and 1 a.m. and a habitual wake time between 6 and 9 a.m. Enrolled participants were asked to maintain their schedule for 1 week before their visit, which was monitored with sleep diaries. In addition, participants were asked to wear an actigraph (Actiwatch Spectrum, Respironics) for one night before their visit. Participants were rescheduled if they reported poor sleep quality in their sleep diary, such as having more than two nights of less than 7 hr of sleep or more than 9 hr of sleep during the week before their visit, or if participants' actigraphy data were showing less than 7 hr of sleep or more than 9 hr of sleep the night before the experimental visit. Rescheduled participants were given another week to fill out a new sleep diary and maintain a regular sleep wake schedule before their visit. Participants were randomized to either have a 2-hr nap opportunity monitored with polysomnography (nap,  $n = 53$ ) or stay awake (wake,  $n = 51$ ), where participants engaged in normal daily activities with activity watch monitoring but were not allowed to have caffeine or take a nap. Participants received monetary compensation for participating in the study.

### WM Task

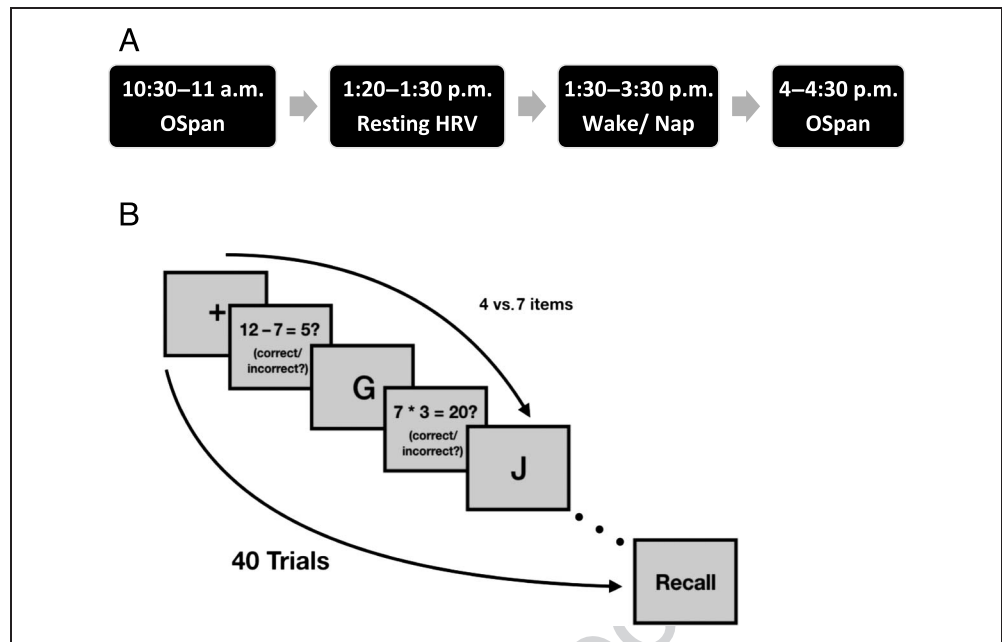
The current study used the OSpan as a measure of WM capacity, which requires participants to solve a series of math operations while memorizing a set of unrelated letters. The task was programmed in MATLAB (The MathWorks Inc., 2015) using Psychtoolbox, which allows random generation

of stimuli every trial. The task included three practice and 40 test trials. Participants were tested in letter strings of four and seven. For each letter string, participants were first shown a series of math problems that they had to confirm were correct or incorrect within 3 sec, using predetermined responses on the keyboard. After each equation, a letter would appear on the screen, and the participant was instructed to remember the letter. At the end of each string, the participant was instructed to recall the letters in the order they were 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 as follows:  $12 - 2 = 8$  (correct/incorrect?) → J;  $6 + 7 = 14$  (correct/incorrect?) → G;  $3 - 2 = 1$  (correct/incorrect?) → S;  $5 + 7 = 13$  (correct/incorrect?) → K (see Figure 1B). 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 one participant in the nap group based on this criterion. We calculated performance as number of correct letters recalled divided by total number of letters in the string per trial, and then we averaged over the total 40 trials. For assessing change in performance from Sessions 1 and 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 hr before and including the study day. Participants filled out sleep diaries for 1 week before the experiment and wore wrist-based activity monitors the night before the study (Actiwatch Spectrum, Philips Respironics) to ensure participants were well rested (at least 7 hr per night). On the experimental day (Figure 1A), participants arrived at the sleep and cognition laboratory at 10:00 a.m. and had EEG electrodes applied, followed by an OSpan WM task. Nap/wake interventions occurred between 1:30 and 3:30 p.m. At 1:30 p.m., nap participants took a polysomnographically recorded nap and were given 2-hr 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, participants were asked not to nap, exercise, or consume caffeine or alcohol and were monitored with actigraphy during the break. Between 4 and 4:30 p.m., all participants were retested on the memory task. Participants completed the Karolinska Sleepiness Scale (KSS; Åkerstedt & Gillberg, 1990) questionnaire two times throughout the experimental day, at the start of each WM task (Sessions 1 and 2) to report their sleepiness. KSS is a 9-point Likert scale often used when conducting

**Figure 1.** Study design and WM task (OSpan). (A) Participants completed the 30-min OSpan WM task at 11:00 a.m. Next, they were randomly assigned to either a nap condition (nap) or a wake condition (wake) that took place between 1:30 and 3:30 p.m. Between 4 and 4:30 p.m., participants repeated the WM task. (B) The OSpan task included three practice and 40 test trials. Participants were tested in letter strings of four and seven. For each letter string, participants were shown a series of math problems that they had to confirm were correct within 3 sec by entering responses on the keyboard. After each equation, a letter would appear on the screen, and the participant 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 the keyboard. Immediately after each trial, the next letter string would be presented.



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-AgCl electrodes placed according to the International 10–20 system. Twenty-two of 32 electrodes were active scalp recordings. The remaining electrodes were used for electrocardiogram (ECG), EMG, EOG, ground, an online common reference channel (at FCz location, retained after rereferencing), and mastoid (A1 and A2) recordings. The EEG was recorded with a 1000-Hz sampling rate, amplified (ActiCHamp), and rereferenced to the contralateral mastoid (A1 and A2) postrecording. Only eight scalp electrodes (F3, F4, C3, C4, P3, P4, O1, and O2), EMG, and EOG were used in the scoring of the nighttime sleep data. High-pass filters were set at 0.3 Hz and low-pass filters were set at 35 Hz for EEG, EOG, and EMG. Raw data were visually scored in 30-sec epochs into wake, Stage 1, Stage 2, SWS (Stages 3 and 4), and REM according to the American Academy of Sleep Medicine manual using HUME, a custom MATLAB toolbox. Before sleep scoring, data were preprocessed using BrainVision Analyzer 2.0 (BrainProducts). EEG recordings were visually scored by two trained sleep technicians. The two technicians scored the same four nap records in this data set independently and reach >85% reliability with each other and one other rater in the laboratory. Minutes in each sleep stage were calculated, and sleep latency were calculated as the number of minutes from lights out until the initial epoch of sleep, Stage 2, SWS, and REM. In addition, 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 divided by the total time spent in bed  $\times 100$ . Durations in each stage were shown in Table 1.

### HRV

ECG data were acquired at a 1000-Hz sampling rate using a modified Lead II Einthoven configuration. We analyzed

**Table 1.** Descriptive Statistics for Nap

	Mean	SEM
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

WASO was calculated as the minutes of wake after first epoch of sleep. All measures are represented in minutes, except for SE, which is in percentage. TIB = total time in bed; TST = total sleep time; SOL = sleep latency (calculated as the time to the first epoch of sleep); SE = sleep efficiency (calculated as  $100 \times \text{TST}/\text{TIB}$ ).



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), 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 laboratory tool. An autoregressive model (model order set at 16; Boardman, Schindwein, Rocha, & Leite, 2002) was employed to quantify the absolute spectral power ( $\text{ms}^2$ ) in the low-frequency (LF) HRV (0.04–0.15 Hz;  $\text{ms}^2$ ) and the HF HRV (0.15–0.40 Hz;  $\text{ms}^2$ ) 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 ( $\text{HF}_{\text{nu}} = (\text{HF HRV}[\text{ms}^2] / (\text{HF HRV}[\text{ms}^2] + \text{LF HRV}[\text{ms}^2])) * 100$ ). Because the LF normalized units are mathematically reciprocal to  $\text{HF}_{\text{nu}}$  (i.e.,  $\text{LF}_{\text{nu}} = 1 - \text{HF}_{\text{nu}}$ ), to avoid redundancy, we computed only the  $\text{HF}_{\text{nu}}$  index, an index often thought to reflect vagal modulation. 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. In addition, 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 prenap wakefulness (wake). Epochs of Stage 1 and WASO were not analyzed, because these periods have not been 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 because of increased stage transitions, this method of HRV analysis decreased the number of participants that could be analyzed.

### Data Reductions

One hundred four (male = 60) young adults were recruited and randomized into the wake condition (51) or the nap condition (53). One participant in the nap condition was excluded based on math accuracy (70%).

Therefore, for the WM task, we have 103 (wake = 51, nap = 52) participants in our data set. For ANS measures, five participants' nap recordings were not collected because of recording computer failures. For Stage 2 sleep, we excluded six participants because of no 3-min window of undisturbed consecutive Stage 2 sleep. For SWS sleep, we excluded 14 participants because of no 3-min window of undisturbed consecutive SWS. For REM sleep, we excluded 30 participants because of no 3-min window of undisturbed consecutive REM sleep. In summary, 47 participants were included in the analyses for wake, 41 participants were included for Stage 2, 33 participants were included for SWS, and 16 participants were included for REM sleep.

### Statistical Analyses

To investigate the within-participant profile of cardiac activity across sleep stages, we used linear mixed effect (LME) models, which do not depend on limiting assumptions about the structure of the variance–covariance matrix (sphericity) or complete data. As the numbers of participants are different among different sleep stages, LME corrects degrees of freedom with Satterthwaite approximation. Our LME model used a within-participants factor of Stage (wake, Stage 2, SWS, REM). All comparisons were adjusted by Bonferroni correction. Effect sizes were calculated using Cohen's *d*. A 95% confidence interval for pairwise comparison was reported.

To confirm that there was no difference in WM baseline performance between the two nap conditions, we used a one-way ANOVA with Condition (wake vs. nap) as the between-participant factor and 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 vs. nap) as the between-participant factor and Test 2 – Test 1 as the dependent variable. We also examined whether sleepiness level changed with different nap conditions. For these analyses, we used a repeated-measure ANOVA with Nap condition (wake vs. nap) as the between-participant factor, Session (1 and 2) as the within-participant factor, and KSS as the dependent variable. Pearson correlation coefficients were used to examine the bivariate relationship between HRV variables of interest and WM performance measures and the relationship between sleep parameters and WM performance as well as the 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 Models 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

Descriptive statistics for sleep architecture were shown in Table 1. Descriptive statistics for autonomic profiles across sleep stages were shown in Table 2.

Prior studies have reported increasing parasympathetic activity from waking to deeper stages of NREM sleep. To test parasympathetic activity across sleep stages, we used an LME model examining HFnu across sleep stages (wake, Stage 2, SWS, REM). We found a stage effect for HFnu,  $F(3, 88) = 30.075, p < .001$ , with a marked increase of vagal tone in SWS, compared with wake ( $p < .0001, d = 1.307, 95\% \text{ CI } [0.1371, 0.2802]$ ) and Stage 2 ( $p < .0001, d = 0.817, 95\% \text{ CI } [0.0578, 0.2075]$ ) as well as REM sleep ( $p < .0001, d = 1.621, 95\% \text{ CI } [0.1582, 0.3386]$ ). Stage 2 sleep showed significantly greater HFnu than wake ( $p = .0257, d = 0.468, 95\% \text{ CI } [0.0068, 0.1452]$ ) and REM sleep ( $p = .0003, d = 0.730, 95\% \text{ CI } [0.0273, 0.2042]$ ) but significantly lower HFnu than SWS. We examined these patterns in the sample of participants that had all sleep stages ( $n = 13$ ); a similar pattern of results was found (Figure 2). Therefore, we

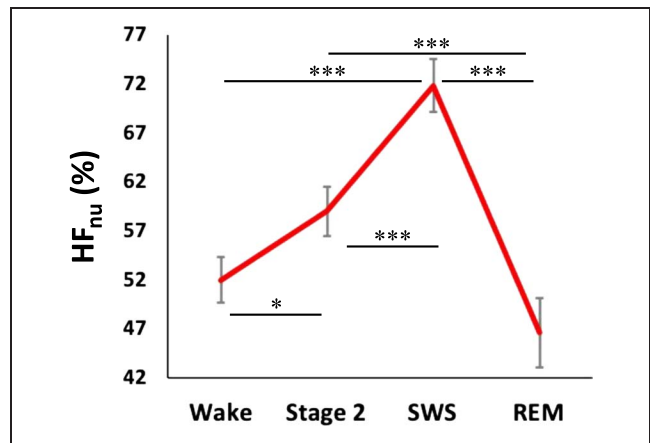
**Table 2.** Summary of HRV Parameters across Sleep Stages

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

Data are reported as Mean. Standard errors are shown in the rows below the mean. Asterisks indicate significant main effects of sleep stages on HRV indices. RR = RR intervals; HF HRV = power in the low-frequency band of the HRV spectrum, often between 0.04 and 0.15 Hz; HF<sub>nu</sub> = HF / (HF + LF)%; N2 = Stage 2 sleep.

\*\*  $p < .01$ .

\*\*\*  $p < .001$ .



**Figure 2.** HRV high-frequency power (HF<sub>nu</sub>) across sleep stages,  $F(3, 88) = 30.075, p < .001$ . Asterisks above bars indicate significant differences between stages (\* $p < .05$ , \*\*\* $p < .001$ ) after adjusting by Bonferroni correction. Error bars represent SEM. Other ANS indices were shown in the Supplemental Figure S1.

presented the full sample results here and in the supplementary files.

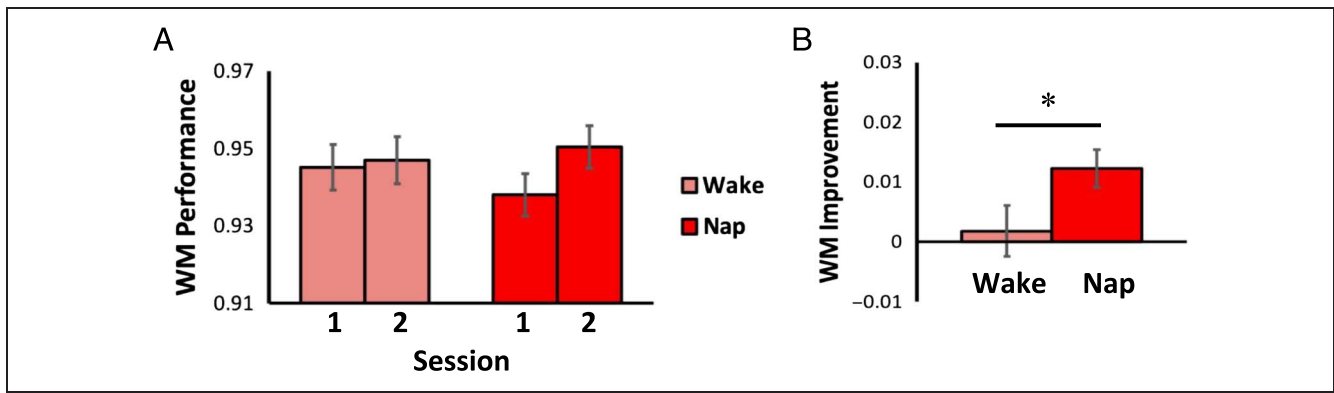
### WM Performance: Comparing Nap vs. Wake Group

Our analysis revealed no significant difference in WM between the two nap conditions at baseline,  $F(1, 101) = 0.79, p = .376, d = -0.216, 95\% \text{ CI } [-0.0231, 0.0088]$ . 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 variable and Test 2 – Test 1 WM performance as the dependent variable. The analysis revealed a main effect of nap condition,  $F(1, 101) = 3.992, p = .04, d = 0.394, 95\% \text{ CI } [0, 0.0208]$ , in which participants showed a greater differential benefit from the nap condition compared to the wake condition (Figure 3).

Repeated-measure ANOVAs revealed no main effect of session or nap condition on sleepiness (KSS) but a significant interaction between session and nap condition,  $F(1, 99) = 5.445, p = .021$ , where the sleepiness levels were lower at Session 2 for the nap group compared to the wake group ( $p = .0088, d = 0.212, 95\% \text{ CI } [-1.003, 0.1293]$ ). Neither the morning nor the afternoon KSS measures were correlated with WM performances (all  $ps > .23$ ). Descriptive statistics for KSS were shown in Table 3.

### Associations between Parasympathetic Activity during Wake and Sleep on WM

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<sub>nu</sub>, and WM performance (baseline and



**Figure 3.** (A–B) WM 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: A 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 ( $*p < .05$ ). Error bars represent *SEM*.

improvement). WM baseline performance was not correlated with  $HF_{nu}$  during Stage 2 sleep ( $p = .150$ ), SWS ( $p = .184$ ), REM sleep ( $p = .092$ ), or wake ( $p = .439$ ). In alignment with our expectation, WM improvement was positively correlated with SWS  $HF_{nu}$  ( $r = .449$ ,  $p = .0145$ ; Figure 4). However, there was no significant associations between WM improvement and  $HF_{nu}$  during Stage 2 sleep ( $p = .503$ ), REM sleep ( $p = .180$ ), or wake ( $p = .584$ ). 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  $ps > .41$ ).

Next, we assessed the importance of ANS activity during sleep for WM performance using hierarchical linear regression. 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  $HF_{nu}$  during SWS. Model 1 was significant,  $F(1, 27) = 70.26$ ,  $p < .001$ , adjusted  $R^2 = .712$ , suggesting that individual difference at baseline has a strong impact on Session 2 performance. Model 2 also significantly predicted performance,  $F(2, 26) = 42.71$ ,  $p < .001$ , adjusted  $R^2 = .749$ ,  $R^2 = 3.7\%$ , with  $HF_{nu}$  as a significant predictor ( $p = .035$ ). Comparing Models 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, WM performance is likely a fairly reliable phenomenon as baseline performance largely predicted Session 2 WM performance; however, adding  $HF_{nu}$  during SWS did provide an increased, albeit small, predictive benefit over baseline WM profiles.

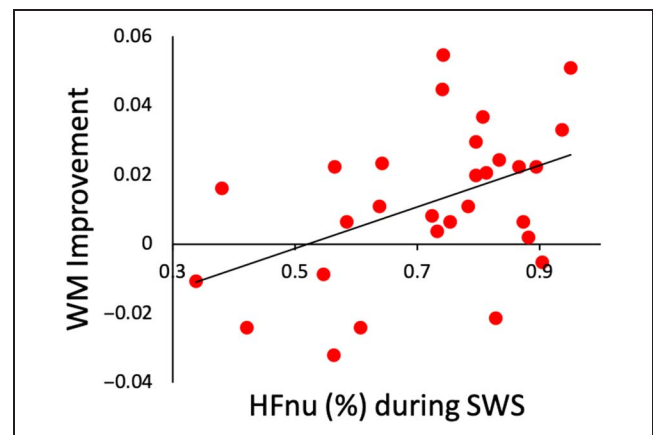
**Table 3.** KSS Scores across the Day

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).

## DISCUSSION

Our health is maintained through variability that allows our biological system to adjust its resources to match specific situational demands. HRV reflects an individual's ability to adapt the ANS to moment-to-moment changes in his or her environment (Thayer & Lane, 2009). 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 (Whitehurst et al., 2018; Cellini et al., 2016; Trinder et al., 2001; Baharav et al., 1995), 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). In addition, participants showed a sleep-dependent boost in WM



**Figure 4.** WM improvement and autonomic activity. Association between WM improvement and  $HF_{nu}$  during SWS ( $r = .449$ ,  $p = .0145$ ). Other HRV indices were shown in the Supplemental Figure S2.

after sleep, and HRV during sleep was associated with WM improvement. In summary, our results provide evidence of a potential role for parasympathetic activity during sleep in WM processing and training in healthy young adults.

### **Nap HRV**

Similar to previous nap (Cellini et al., 2016) and nighttime sleep (Whitehurst et al., 2018) studies, 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, Waloszek, Woods, & Jordan, 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). The current findings suggesting parasympathetic increases during a daytime nap may support WM improvement have implications for potential interventions targeting parasympathetic activity during sleep in WM training paradigms. Considering that the most common reason for napping in healthy young adults seems to be for restorative purposes (Duggan, McDevitt, Whitehurst, & Mednick, 2018), these data suggest that daytime naps may provide a compensatory protective window for the cardiovascular system (Naska, Oikonomou, Trichopoulou, Psaltopoulou, & Trichopoulos, 2007) and serve as a “mini cardiovascular break” that might potentially benefit psychological and physiological health.

### **Nap and WM: The Functional Roles of Cardiac Activities**

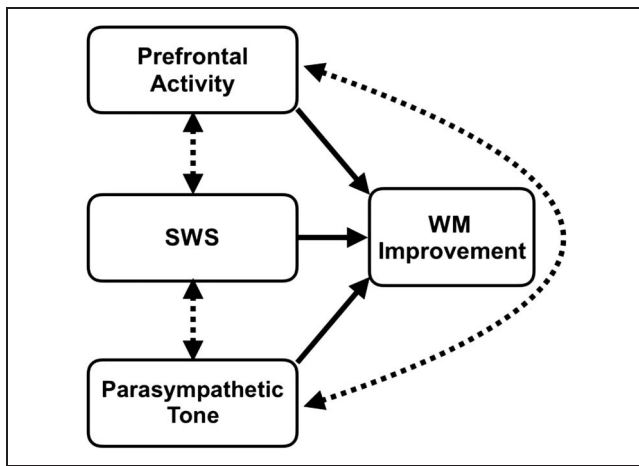
Whereas a large body of studies has demonstrated the negative impact of sleep loss preceding WM performance (Pasula et al., 2018; Goel et al., 2009; Choo et al., 2005), studies into the effect of posttraining sleep on WM improvement are few, and none has examined this question in the context of ANS activity. We show that, compared with wake, WM improves after a daytime nap, similar to prior studies using a nap (Lau et al., 2015) and nocturnal sleep (Zinke et al., 2018; Kuriyama et al., 2008), suggesting that sleep might provide an optimal brain state that facilitates WM training. We did not, however, find a significant correlation between waking HRV (as assessed with RMSSD, HF HRV, and HF<sub>nu</sub>) 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 (1) based on median splits of the data on HRV or WM performance, (2) based on HRV measured during or before WM task with participants sitting in front of a computer, and (3) based on WM performance measured under high pressure (Mosley et al., 2018; Giuliano, Gatzke-Kopp, Roos, & Skowron, 2017; Spangler & Friedman, 2017; Laborde, Furley, & Schempp, 2015; Hansen et al., 2003, 2004). 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). The current study failed to replicate either the prior literature on waking HRV and WM baseline performance based on either median split or linear correlation. The discrepancy between the current study versus previous literature is likely because of the way that HRV was measured, during or near testing in a seated position versus supine preparing for sleep. Specifically, previous studies measured HRV during the WM task or right before the task and showed a relation between waking HRV and WM performance. In contrast, HRV in the current study collected data at least 2 hr after WM Session 1, and participants were lying down in bed preparing to take a nap. Future studies should record HRV at cognitive testing as well as at prenap resting to further elucidate the relationship between resting HRV and cognition. 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.

### **Biomarkers of WM Function: SWS, Parasympathetic Activity, and Prefrontal Functioning**

We propose a conceptual model (Figure 5) 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 pFC (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





**Figure 5.** Conceptual model: Here, we illustrate the interaction between three biological markers, prefrontal brain activity, SWS, and parasympathetic tone, which together and/or independently lead to WM improvement in young adults.

wake in both young and older adults (Yoo et al., 2018). In addition, 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.

One important subfield in which these interacting features may be especially salient is aging. Aging is characterized by a decline in executive functions (Kirova, Bays, & Lagalwar, 2015), prefrontal brain atrophy (Mander et al., 2013; Salat et al., 2004), impaired sleep (Mander, Winer, & Walker, 2017), and decreased vagal tone (O'Brien, O'Hare, & Corral, 1986). Although 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.

### Limitations

The current study has several limitations that need to be addressed. First, one limitation of this study is the relatively small effects size ( $d = 0.394$ ) when comparing the WM improvement between the wake group and the nap group. However, we did not expect a large effect size given that WM has been traditionally considered to be inflexible.

Although recent studies report that WM capacity is subject to plastic changes, WM training typically requires weeks or months of training, and there is a large variation in effect size in prior WM training studies. For example, a meta-analysis (Melby-Lervåg & Hulme, 2013), including studies where participants underwent 2–7 weeks of WM training, showed that effect sizes comparing pretest–posttest gains between WM training groups and control groups ranged from  $d = 0.72$  to  $d = 0.84$  on verbal WM measures and from  $d = 0.44$  to  $d = 0.55$  on visuospatial WM measures. Taken together, the amount of improvement examined in the current study is the change after a nap versus wake, whereas other WM training studies examined changes over weeks or months of daily trainings comparing to nontrained controls. Hence, although the effect size we revealed was smaller than those in previous WM training studies, such amount of improvement given a period of daytime sleep still provides implications for sleep as a potential intervention on WM functions.

Another limitation is the reduction in participant numbers because of HRV methodological constraints. The current study has several limitations that need to be addressed. First, one limitation of this study is the reduction in participant numbers because of HRV methodological constraints. Specifically, standard practice for HRV analyses requires assessment of HRV over a 5-min period of a consistent sleep stage, according to the Task Force of the European Society of Cardiology, the North American Society of Pacing Electrophysiology (1996). However, several studies have presented data with shorter epoch windows and demonstrated robust results. For example, a recent study in our group has used a 3-min window of undisturbed sleep (Whitehurst et al., 2018) and showed similar HRV profiles in a daytime nap and nocturnal sleep as the previous literature, which also suggested that 3-min windows were able to capture HRV profiles in different sleep stages. Furthermore, a review article by Shaffer and Ginsberg (2017) pointed out that the minimum recommended periods were 2 min for LF and 1 min for HF. Therefore, our 3-min windows that contain about 27–72 complete periods of oscillation in the HF band and 7–27 complete periods of oscillation in the LF band provide a fair amount of HRV. More importantly, the 3-min windows were chosen based on the cost–benefit trade-off that we encountered with the nap study design. In nap studies, sleep is more fragmented with a large amount of stage transitions, and thus, using 5-min windows would have decreased the number of available participants (only 23 nap participants have HRV data during SWS) and would have likely have biased the sample toward less fragmented sleepers. However, we considered the strength of the nap design (Mednick, Nakayama, & Stickgold, 2003): (1) control for circadian confounds and (2) better wake control versus sleep deprivation overnight; these benefits outweighed the potential problems from fragmented sleep and shorter HRV windows in the current study. However, to retain more statistical

power, future studies should confirm these results in HRV assessments during nocturnal sleep that will afford longer window lengths. In general, the HRV methodology emphasizes consolidated sleep stages (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), and because naps have more fragmented sleep because of increased stage transitions, even 3 min of undisturbed sleep in each sleep stage is not as common in daytime naps in our participants.

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 HF<sub>nu</sub> only, whereas the other markers of parasympathetic activity, although in a similar positive direction, did not reach statistical significance. This discrepancy may have been because of low power within certain sleep stages and should be further investigated in a nighttime sleep study, which provides longer bouts of deep sleep.

## Conclusion

This study investigated the role of sleep HRV during a daytime nap in WM performance across the day. We showed the first evidence that the autonomic activity during sleep, but not wake, played a crucial role in WM. Thus, for healthy young adults, a daytime nap can serve as a “mini cardiovascular break” that benefits executive functions.

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