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An increase in sleep slow waves predicts better working memory performance in healthy individuals☆

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ABSTRACT

Sleep is imperative for brain health and well-being, and restorative sleep is associated with better cognitive functioning. Increasing evidence indicates that electrophysiological measures of sleep, especially slow wave activity (SWA), regulate the consolidation of motor and perceptual procedural memory. In contrast, the role of sleep EEG and SWA in modulating executive functions, including working memory (WM), has been far less characterized. Here, we investigated across-night changes in sleep EEG that may ameliorate WM performance. Participants (N = 25, M = 100%) underwent two consecutive nights with high-density EEG, along with N-back tasks, which were administered at three time points the day before and after the second night of sleep. Non-rapid eye movement sleep EEG power spectra, power topography, as well as several slow-wave parameters were computed and compared across nights. Improvers on the 1-back, but not non-improvers, showed a significant increase in SWA as well as in down slope and negative peak amplitude, in a fronto-parietal region, and these parameters increases predicted better WM performance. Overall, these findings show that slow-wave sleep has a beneficial effect on WM and that it can occur in the adult brain even after minimal training. This is especially relevant, when considering that WM and other executive function cognitive deficits are present in several neuropsychiatric disorders, and that slow-wave enhancing interventions can improve cognition, thus providing novel insights and treatment strategies for these patients.

1. Introduction

Consolidated, restorative sleep is an essential component of brain health. Studies have consistently shown that acute and chronic sleep disruption impair multiple domains of executive function, including vigilance, attention, multiple domains of learning and memory, decision making, and response inhibition (Banks and Dinges, 2007; Chee and Tan, 2010; Durmer and Dinges, 2005; Kacha et al., 2003; also see Lowe et al., 2017; Whitney et al., 2017; Zinke et al., 2018). Identifying sleep-specific features that support cognitive performance – and more broadly, brain health – can elucidate modifiable biological targets for cognitive enhancement (Friedl et al., 2016; Hertzog et al., 2008; Sreekumar et al., 2017). In addition, this line of inquiry bears significant potential for public health impact given the pervasiveness of insufficient sleep in the general population (http://aasm.org/resources/pdf/pressroom/adult-sleep-duration-consensus.pdf), and inherence of acute and chronic sleep disruption in high-tempo, high-risk occupations, such as the Armed Forces and critical incident responders (e.g., Lentino et al., 2013; MacMillan et al., 2017; Mysliwiec et al., 2016; Parker and Parker, 2017; Williams et al., 2014; Wolkow et al., 2015).

Sleep is a complex neurophysiological phenomenon characterized by distinct states, rapid-eye movement (REM) sleep and non-REM (NREM) sleep, and each differentially influences cognitive functions. Each sleep state also has unique features that may support cognitive performance.

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Slow-wave sleep is an important stage of NREM sleep, and slow-wave activity (SWA; 0.5–4 Hz) is a global index of the sleep homeostasis (Achermann and Borbely, 2003; Borbely, 2001; Borbely and Achermann, 1999). Furthermore, SWA may reflect localized experience-dependent cortical plasticity (e.g., Huber et al., 2004b; Kuhn et al., 2016; Miyamoto et al., 2017; Murphy et al., 2011; Pugin et al., 2015; Rodriguez et al., 2016). Specifically, fronto-parietal increases in SWA following working memory and visuomotor tasks have been observed in children and adults (Aeschbach et al., 2008; Landsness et al., 2009; Wilhelm et al., 2014). Alternatively, deprivation of slow-wave sleep prevents improvements in cognitive performance (Aeschbach et al., 2008; Landsness et al., 2009; Lowe et al., 2017; Zinke et al., 2018). Furthermore, specific features of SWA, including slow oscillations (SO; 0.5–1 Hz), may be implicated sleep-dependent memory consolidation and performance (Anderson and Horne, 2003). The slope (time derivate) of the SO reflects the amount of transmembrane neuronal currents underlying the generation of inhibitory (down-slope) and excitatory (up-slope) post-synaptic potentials, whereas the peak amplitude of the SO is modulated by the strength and synchronization of cortical neurons, as demonstrated by both animal and modeling data (Esser et al., 2007; Vyazovskiy et al., 2007). Together, these observations suggest that changes in experience-induced changes in SWA may not only support efficient cognitive processes, but that SWA enhancement methods may offer new strategies to preserve or optimize cognitive performance in healthy and clinical samples (e.g., Bellesi et al., 2014; Brunoni and Vanderhasselt, 2014; Vyazovskiy and Tobler, 2008; Walsh et al., 2006).

In this study, we hypothesized that adult participants who show improved performance on a working memory task over a two-day period would also show a significant increase in SWA compared to non-improvers. Working memory refers to the cognitive process that maintains, manipulates and updates incoming information (Cowan, 2008; Jaeggi et al., 2008) in real time to guide proximal decision-making and behavioral responses. In adults, performance on working-memory tasks can improve with practice (Clark et al., 2017; Jaeggi et al., 2008; Mewborn et al., 2017). Furthermore, it was recently reported hat both children and adults showed an overnight improvement in the N back, a working memory task, after just three training sessions. However, the extent to which performance improvements are associated with SWA is unclear (Kuriyama et al., 2008; Zinke et al., 2018). Thus, the objective of the study was to assess the relationship between performance on the N-back task (Kirchner, 1958) and specific features and localization of SWA.

2. Methods

2.1. Participants

Eligible participants were military active-duty service men between the ages of 18–50, who were previously deployed in support of the Global War on Terror. Participants were recruited through a diverse recruitment strategy, which included flyers, television and online advertisements, and placement of promotional materials at local military units. Interested individuals contacted the research coordinator by telephone, and received additional information about study aims, procedures, risks, and compensation. They were asked to provide verbal consent prior to answering questions to determine eligibility. Those who remained eligible after the telephone screen were invited for an in-person visit, where they provided written, informed consent prior to completing additional screening procedures.

2.2. Assessment of eligibility

Eligible participants were free from medications known to affect sleep/wake functioning for at least 2 weeks prior to study enrollment. Participants also had to consume no more than 2 cups of caffeine per 24 h and drink, on average, no more than 2 alcohol drinks per day or 14 drinks per a 2-week period. Exclusion criteria included: a history of a psychotic or bipolar disorder; substance or alcohol abuse within the previous 3 months; current diagnosis of untreated severe depression; current post-concussive symptoms and/or rehabilitation treatment for traumatic brain injury; significant or unstable acute or chronic medical condition; or a current sleep disorder other than insomnia or nightmares.

Screening procedures included self-report questionnaires to assess sleep quality and disruptive nocturnal behaviors, symptoms of post-traumatic stress disorder (PTSD) and depression, alcohol and substance use. These symptom domains were assessed using the Pittsburgh Sleep Quality Index PSQI (Buysse et al., 1989) and PSQI-A Addendum for PTSD (Germain et al., 2005; Insana et al., 2013), Insomnia Severity Index ISI (Bastien et al., 2001), the Epworth Sleepiness Scale ESS (Johns, 1991), the Patient Health Questionnaire-9 item version PHQ-9 (Kroenke et al., 2001), and PTSD Checklist (PCL-5) for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition DSM-5 (Narrow et al., 2013).

The PSQI is a self-report measure of sleep quality over the past month (Buysse et al., 1989), which consists of 19 items from 7 components which produce a global score ranging from 0 to 27. Greater global scores indicate poorer sleep quality, and a global score >5 is used as a clinical cutoff point. The PSQI-A (Germain et al., 2005; Insana et al., 2013) is a self-report questionnaire developed at the University of Pittsburgh to assess the presence and frequency of seven disruptive nocturnal behaviors common in PTSD. Participants rate the frequency of nocturnal behaviors using a 4-point Likert scale ranging from '0' = no disturbance and '3' = occurring three or more times a week. A total score ranging from 0 (normal) to 21 (severe) is calculated and a cut off score of >4 is used to discriminate adults with and without PTSD. The ISI is a 7-item self-report scale designed to measure the nature, severity, and impact of insomnia within the last two weeks (Bastien et al., 2001). Participants rate their responses on a five-point Likert scale ranging from '0' = not at all to '4' = extremely. Total scores range from 0 to 28, with higher scores indicating greater insomnia severity. A cutoff score of >8 is generally used to indicate significant insomnia. The PHQ-9 (Kroenke et al., 2001) is a brief screening tool for depression using DSM diagnostic criteria (American Psychiatric Association, 2013). A total score of symptom severity ranging from 0 to 27 is calculated, where higher scores indicate greater severity of depressive symptoms. Cut off scores of 5 (mild depression) and 10 (moderate depression) are typically used to determine the need for depression treatment in clinical settings. The ESS is a widely used self-report measure of daytime sleepiness (Johns, 1991). The ESS asks individuals to rate how sleepy they would become during eight scenarios on a scale from '0' = no chance of dozing to '3' = high chance of dozing. A total score from 0 to 24 is used, with higher scores indicating greater levels of daytime sleepiness. A cutoff score of 10 or greater suggests significant daytime sleepiness and the potential presence of sleep-disordered breathing. Finally, the PCL-5 (Weathers et al., 2013) is a 20-item self-report screening measure for the 20 DSM-5 symptoms of PTSD (Narrow et al., 2013). The PCL-5 generates a total symptom severity score ranging from 0 to 80 and individual symptom cluster scores, where higher scores indicate greater PTSD symptom severity. Preliminary validation work suggests that a cut-off point of 33 on the PCL-5 differentiates those with and without PTSD. As shown in Table 1, mean scores on all self-report scales were below previously published thresholds for clinical significance.

To ascertain or rule out the presence of PTSD or other psychiatric disorders, participants also completed structured interviews with a trained assessor. PTSD was assessed using the Clinician Administered PTSD Scale CAPS (Blake et al., 1995). Only participants who did not meet diagnostic criteria for PTSD and who did not endorse significant symptoms as indicated by a total CAPS score of ≤ 20 were used in the present analyses.

Other current and past psychiatric disorders were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I (First et al., 1996). Finally, the presence of sleep disorders was determined using a structured clinical interview (Buysse et al., 2008, 2011; Germain

et al., 2006, 2012) developed at the University of Pittsburgh to assess the presence, frequency, and severity of sleep disorders symptoms. Participants who met criteria for a current sleep disorder, other than insomnia or nightmares, were ineligible for study participation and referred for a sleep evaluation. The absence of sleep disordered breathing was further confirmed by in-home overnight testing using the ApneaLink Plus device (ResMed, 2017).

2.3. Laboratory procedures

The study designed is depicted in Fig. 1. Participants (N = 25, see Table 1 for demographic and clinical measures) reported to the sleep laboratory at 20:00 on Night 1 and remained in the laboratory for the following 48 h. Upon arrival, they were fitted with a 64-channel high-density electroencephalography (hd-EEG) montage (Electrical Geodesics Inc, 2017). Participants were allowed to sleep undisturbed from 23:00 until 07:00. Overnight sleep records were scored using the American Academy of Sleep Medicine (AASM) criteria (Iber et al., 2007).

After removing the hd-EEG montage in the morning, participants were provided with a light breakfast. Participants were then fitted with a standard 10-electrode AASM montage for multiple sleep latency tests (MSLT) completed during the day, every 2 h starting at 09:00 until 19:00. The MSLT was performed because sleep latency is considered a reliable indicator of daytime sleepiness resulting from disturbed sleep. We could therefore confirm that all participants were normal sleepers. Furthermore, participants were awoken immediately after falling asleep (e.g., following 30 s spent in N1 sleep) to avoid any daytime NREM sleep N2-N3, which were used to assess overnight sleep effects on cognitive performance. They were unwired after the last MSLT at 19:30, and the full hd-EEG montage was fitted again at 21:00. The procedures were repeated on Night 2 and the following day until discharge at 20:00.

2.4. Working memory task

On Day 1 and Day 2, participants completed the N-back task at 11:20, 15:20, and 19:20. The N-back paradigm is a widely used measure of working memory performance (Owen et al., 2005). Furthermore, a recently published study with a similar paradigm involving the same working memory task (N-Back), demonstrated an overnight performance improvement in both children and adults (Zinke et al., 2018) Participants were asked to monitor a series of squares presented at different locations on a computer screen and press the number '2' key on the keyboard with their right index finger when the square was displayed in the position presented 'n' trials previously. For all other trials, participants were told to press the number '3' key on the keyboard with their right middle finger. The N-back presents three different 'n' conditions. For the 1-back condition, participants were instructed to press the button when the square appeared in the same position it appeared in the previous trial. For the 2-back condition, participants were instructed to press the button when the square appeared in the same position it was presented two trials prior. Finally, for the 0-back condition, participants were simply asked to press the button when the square appeared in the top left corner of the screen. After instructions were given, participants were presented with 30-sec blocks of 0-back, 1-back, and 2-back stimuli in a randomly assigned order. Between blocks, a fixation cross was displayed on the screen during 15-sec rest periods. The n-back task had 144 trials and was run two times for a total of 288 trials per time point to increase power. The task runs for a total of seven minutes. The N-back records reaction time (RT, in milliseconds) and accuracy for each trial (correct trial, CT), which can be averaged across all trials.

Participants were classified as "improvers" or "non-improvers" for analysis of performance accuracy and reaction time on the N-back tasks. Performance data from each Day 1 N-back trials were averaged across the three assessment time points; Day 2 measures were also averaged. We decided to compute and compare the average of the three sessions of each day for two reasons. First, if the increase in slow waves was related to the training occurring during the WM task, the best way to capture this increase was taking in account all sessions, rather than just the last one before sleep. Furthermore, by comparing averaged performances from the two days we could subtract common daytime practice effects. To assess changes in performance accuracy on the N-back tasks, an "improver" was defined as averaging 1 or more additional correct response during each of the three 48-trial sessions on Day 2 relative to Day 1. Specifically, in order to qualify as an improver each participant had to show an increase of at least one point on the average correct responses across the three daytime sessions in the second day of assessment relative to the first day (e.g., improve from an average correct response score of 44–45). To assess performance change in reaction time in all N-back conditions, an "improver" averaged a faster reaction time on Day 2, and a "non-improver" averaged a slower reaction time on Day 2.

Table 1
Demographic and clinical measures for the study group (N = 25).

	Statistics
	% (n)
% men (n)	100 (25)
% Caucasian (n)	88 (22)
% not Hispanic or Latino	88 (22)
	Mean ± SD
Age	33.47 ± 7.44
Apnea-Hypopnea Index (AHI)	2.80 ± 2.83
Clinical Administered PTSD Scale Score (CAPS)	11.04 ± 7.75
PTSD Checklist for DSM-5 (PCL-5)	22.24 ± 6.94
Patient Health Questionnaire (PHQ-9)	1.60 ± 2.81
Pittsburgh Sleep Quality Index (PSQI)	4.08 ± 2.75
PSQI-Addendum for PTSD (PSQI-A)	1.28 ± 2.21
Insomnia Severity Index (ISI)	3.92 ± 4.33
Epworth Sleepiness Scale (ESS)	4.24 ± 2.37

2.5. Sleep EEG scoring and data processing

Sleep scoring was performed according to AASM criteria (Silber et al., 2007). Whole night sleep EEG data were processed in MATLAB R2015 (The MathWorks Inc., Natick, MA). All signals were filtered using a 0.5 Hz high-pass filter and 40 Hz low-pass filter, then down-sampled to 128 Hz and re-referenced to the average of all 64 channels. The sleep recording was then divided in 6-s epochs. N2 and N3 NREM epochs, where most slow wave activity occur, were selected. Semiautomatic artifact rejection procedures were utilized to remove channels and epochs with high-frequency noise or other persistent artifacts (i.e., low-frequency drift due to poor channel contact). Specifically, thresholds were automatically calculated for low (1–4 Hz) and high (20–30 Hz) frequency ranges at the 99.8th and 99.5th percentile, respectively, for each channel. Then, spectral power in the low (1–4 Hz) and high (20–30 Hz) frequency ranges across all 6-sec NREM epochs were plotted and visually inspected for each channel. Channels with artifacts affecting a majority of the recording were removed. Furthermore, topographic plots were used to identify channels, which showed distinctly greater power relative to neighboring channels. Overall, more than 75% of the data recorded for each participant and more than 90% of the channels were retained after this procedure.

Spectral power density was computed using Welch's modified periodogram method (i.e., *pwelch* function in MATLAB) in 2-s Hamming windows (50% overlap) to decompose EEG time-series signals into the frequency domain in the 0.5–40 Hz range. To better characterize SWA (0.5–4 Hz), we also employed an in-house algorithm (Ferrarelli et al., 2010a; Riedner et al., 2007) for the automatic detection of several slow wave parameters. Specifically, each EEG signal was referenced to the average of the two mastoid channels and band-pass filtered at 0.5–4.0 Hz. Then, slow waves were detected as negative deflections between two zero crossings. Only waves with 0.25- to 1.0-second consecutive zero crossings detected in artifact-free non-REM epochs were considered slow waves. Four slow-wave parameters were computed: down slope, defined

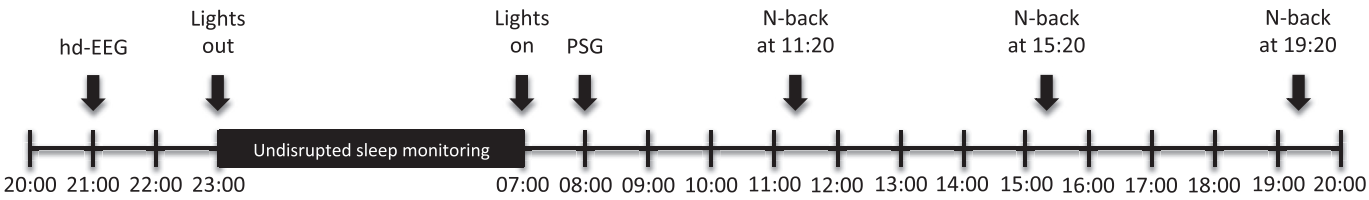

Fig. 1. Study experimental design.

as the amplitude of the most negative peak divided by the time from the previous (first) zero crossing; negative peak amplitude, as the most negative amplitude following the first zero crossing; up slope, defined as the amplitude of the most negative peak divided by the time until the next (second) zero crossing; and slow-wave density, defined as the number of slow waves detected per minute of NREM sleep. For additional details, refer to Ferrarelli, Riedner and colleagues (Ferrarelli et al., 2010b; Riedner et al., 2007).

2.6. Statistical analyses

To compare sleep architecture and NREM sleep EEG power spectra across nights, paired t-tests were computed. Topographic differences in sleep slow wave power as well as in other slow wave parameters were assessed with Statistical Nonparametric Mapping (SnPM), a statistical approach that enables corrections for multiple comparisons. Furthermore, correlation analyses between slow wave parameters and across nights N-back performance changes were performed.

3. Results

3.1. Sleep architecture and MLST

There were across night differences in some sleep architecture parameters, which included greater total sleep time, sleep efficiency, and REM sleep on Night 2, as well as reduced NREM N1 sleep and waking after sleep onset (WASO) on Night 2 compared to Night 1. In contrast, there were no between-night significant differences in NREM N2 or N3 (Table 2). Similarly, no across night differences were found in N2 and N3 in improvers and not-improvers for the different N back tasks.

As a group, subjects showed no significant change in EEG power across all frequencies from Night 1 to Night 2. There was a slight increase in delta power at Night 2, which, however, was not significant. We also found that mean daily sleep latency values were comparable across days (min. = 10 ± 1.7; and min. = 10 ± 1.5 respectively), and within the range reported in normal sleepers.

Table 2
Mean (and standard deviations) sleep parameters for Night 1 and Night 2 in study participants.

Sleep Parameter	Night 1	Night 2	t statistics	*p*-value
Total sleep time (min)	405.28 (37.76)	425.54 (38.37)	3.0	0.005
% Sleep efficiency	82.90 (7.84)	86.49 (7.66)	3.25	0.003
Sleep latency (min)	23.80 (23.35)	16.20 (16.42)	−2.0	*n.s.*
Stage N1 sleep (min; %)	46.4; 11.82%	39.2; 9.55%	−2.9	0.007
	(20.7; 6.12%)	(19.3; 5.50%)	−2.3	0.01
Stage N2 sleep (min; %)	227.0; 56.02%	227.2; 53.63%	−1.8	*n.s.*
	(36.2; 6.96%)	(30.5; 6.97%)	−2.0	*n.s.*
Stage N3 sleep (min; %)	57.6; 12.80%	62.0; 14.34%	1.8	*n.s.*
	(30.8; 7.34%)	(35.0; 7.90%)	2.0	*n.s.*
REM sleep (min; %)	79.3, 19.36%	97.0; 22.49%	2.9	0.008
	(26.2; 5.79%)	(31.3; 6.26%)	2.8	0.009
Waking after sleep onset (min; %)	59.4; 12.42%	44.6; 9.27%	−2.5	0.02
	(37.8; 7.83%)	(36.5; 7.59%)	−2.7	0.01

3.2. N Back performances

We found that only a small subset (N = 5) of the 25 all-male subjects showed an across night improvement in accuracy in the 0 Back task, which was very modest (1.7 ± 1.5 out of 48), largely due to ceiling performances at baseline. In contrast, both in the 1 Back and the 2 Back there was a similar number of improvers (N = 11 and N = 14, respectively) relative to non-improvers (Table 3). Furthermore, in the 1 Back improvers showed ~10% increase in performance (4.4 ± 1.2 out of 48), while non-improvers had a small decrease (−1.0 ± 1.0) from day one to day 2. In the 2 Back, improvers had a smaller, more variable increase in performance (3.3 ± 2.2 out of 48) compared to the 1 Back, whereas non-improvers had a slight reduction in performance (−1.0 ± 1.2). To assess whether across group overnight changes in performance were driven by pre-sleep differences, we calculated and compared baseline performance values (averaged across the first three daytime sessions) for improvers and not-improvers in each N Back. We found that these values did not differ between groups (0 Back impr. = 45.5 ± 1.3, not impr. = 46.4 ± 2.0, p = 0.61; 1 Back impr. = 42.8 ± 4.2, not impr. = 43.4 ± 4.9, p = 0.78; 2 Back impr. = 41.2 ± 5.7, not impr. = 43.9 ± 4.9, p = 0.3). Additionally, RT improved in virtually all study participants across N-Back tasks, with N = 23 for 0 (−69 ± 57) and 1 (−81 ± 57) Back, and N = 22 for the 2 (−30 ± 38) Back.

3.3. Sleep EEG power analyses

We first investigated NREM sleep EEG activity in all study participants. Power spectra analyses showed no differences between Night 1 and Night 2, with the exception of a modest increase in the delta, or SWA (1–4.5 Hz) range, which, however, failed to reach significance (Supp. Figure 1A). Similarly, topographic analyses in several frequency bands, including delta, theta, alpha, sigma, beta, and gamma, showed no across night differences (Supp. Figure 1B). We then assessed whether sleep EEG activity was differentially modulated in individuals showing an improvement in the N back tasks compared to those who did not. Since virtually all participants showed an improvement in the 0 Back performance, as well as in RT across N-Back tasks, we focused on the 1 Back and the 2 Back CT. We found a significant increase in the EEG power spectra of the improvers in the 1 Back task, but not in the non-improvers, which was specific for SWA (Fig. 2A). Topographic analyses revealed that the 1 Back task improvers had a SWA increase during Night 2 compared to Night 1, which was particularly prominent (25–30%) in a right fronto-parietal area (N = 18 electrodes), where it reached significance even after correction for multiple comparisons ($p < 0.05$, SnPM), whereas non-improvers showed no increase across night SWA modulation (Fig. 2B). Furthermore, in the 1 Back improvers we found that slow wave enhancement was even more dramatic in the first sleep cycle (~60%

Table 3
N-Back task improved and not-improved subjects.

N Back Task	0-Back	1-Back	2-Back
Improvers (N)	5	11	14
Performance change (M±SD)	1.7 ± 1.5	4.4 ± 1.2	3.3 ± 2.4
Non-Improvers (N)	20	14	11
Performance change (M±SD)	−0.5 ± 1.0	−1.0 ± 1.0	−1.0 ± 1.2

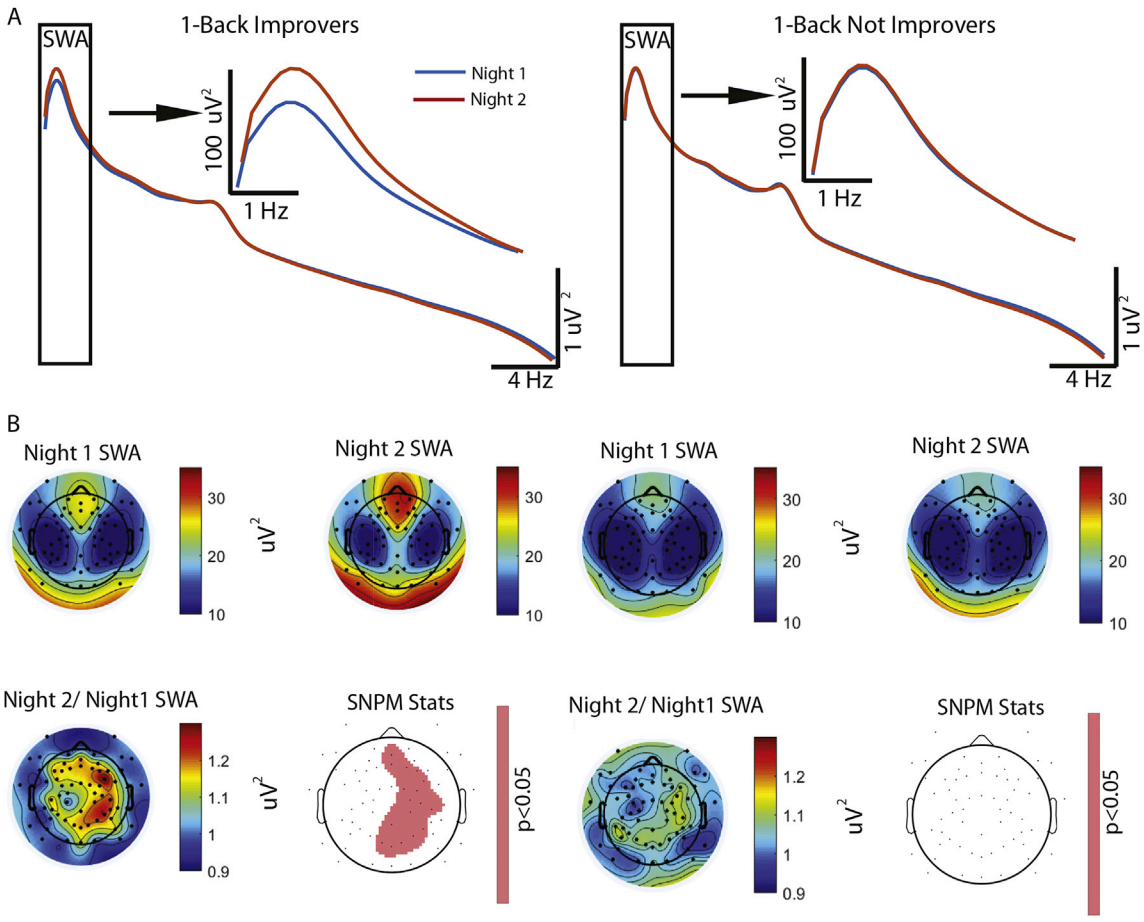

Fig. 2. A significant across night increase in Slow Wave Activity (SWA, 0.5–4 Hz NREM sleep power) was present in N1 back improvers, but not in not improvers. **A:** NREM sleep EEG average power spectra for Night 1 (red) and Night 2 (blue) in individuals who showed an improvement in the N1 Back task (Left) and those who did not (right). Of note, only in the improvers there was an increase in NREM sleep power, which was specific for the SWA (as shown in the insets). **B:** Topographic plots of SWA for N1 Back improvers (left) and non-improvers (right) showed a SWA increase only in the improvers, which was maximal in a large fronto-parietal area and was significant after correction for multiple comparisons (Statistical nonparametric Mapping, SnPM, $p < 0.05$).

increase, Supplementary figure 4), which is when slow wave activity is most prominent. An increase in SWA was also observed in the power spectra of the 2 Back task improvers (Supplementary Figure 2A). This SWA enhancement was localized to the same fronto-parietal area activated by the 1 back (Supplementary Figure 2B) but was less prominent (15–20%) and failed to reach significance after correction for multiple comparisons ($p > 0.05$, SnPM).

3.4. Sleep slow wave parameter analyses

To better characterize which aspects of SWA were enhanced in the 1-Back improvers, four slow wave parameters were examined: down slope, negative peak amplitude, up slope, and slow wave density, as described in the methods and shown in Fig. 3A. We found an increase in the slow wave down slope from Night 1 to Night 2, which was particularly prominent in the same fronto-parietal region showing enhanced SWA. This increase involved 26 electrodes and was significant even after correction for multiple comparisons (Fig. 3B, $p < 0.05$, SnPM). A fronto-parietal increase was also observed for the slow wave negative peak amplitude ($N = 25$ electrodes), which was significant in Night 2 compared to Night 1 (Fig. 3B, $p < 0.05$, SnPM). In contrast, no significant across night increase was found for either the up slope or the slow wave density (Supp. Figure 3). To confirm that these effects were specific for the 1-Back improvers, we examined the same slow wave parameters in the non-improvers and found that none of them was significantly modulated between Night 1 and Night 2 (data not shown).

3.5. Correlation between sleep slow waves and 1-back performance

To further investigate the link between sleep slow waves and task performance, correlation analyses were performed. We found that across night modulation of SWA was significantly associated with changes in 1-Back performance across all subjects ($R = 0.48$; $p = 0.01$), and that this association was strongest in 1-Back improvers ($R = 0.75$; $p = 0.008$), consistent with a positive effect of enhanced SWA on task performance (Table 4). Positive correlations were also established for the down slope and the negative peak amplitude ($R = 0.41$; $p = 0.03$ and $R = 0.48$; $p = 0.03$, respectively) in all study participants, which were again most significant for the 1 Back improvers ($R = 0.56$; $p = 0.02$ and $R = 0.71$; $p = 0.01$, respectively, Table 4).

4. Discussion

In this study we collected whole night sleep hd-EEG recordings in 25 all-male healthy subjects before and after Working Memory (WM), N back tasks. We found that the 1 back improvers had significant across night increases in SWA, slow wave down-slope, and negative peak amplitude in a right fronto-parietal region. These slow wave parameter increases were not observed in those who did not improve. Furthermore, across night variations in slow wave parameters predicted overnight performance changes in all study participants.

A first important finding of this study is the involvement of sleep SWA in ameliorating WM. Sleep is involved in the consolidation of procedural

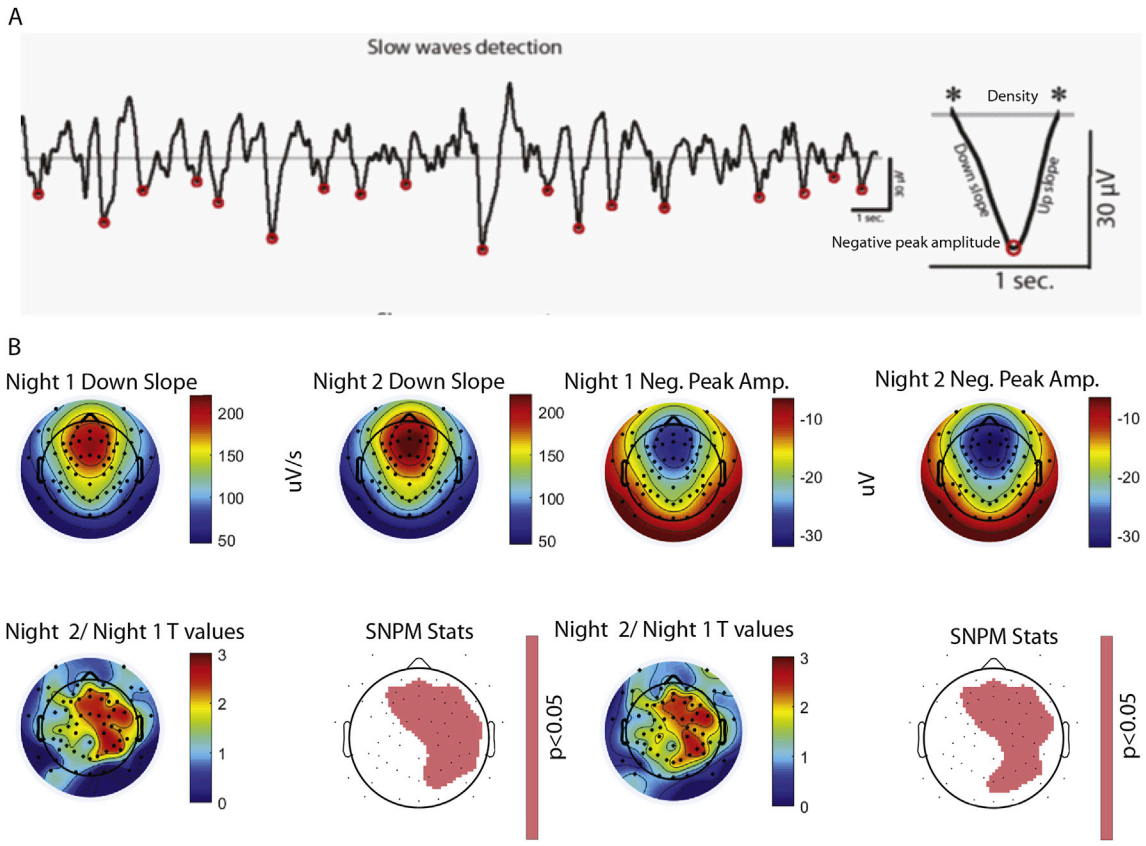

Fig. 3. N1 Back improvers showed a significant across nights increase in slow wave parameters, including slow wave down-slope and negative peak amplitude. **A:** A slow wave detection algorithm was employed to characterize the slow wave parameters implicated in the SWA increase observed in N1 Back overnight improvers. **B:** Topographic plots demonstrated across nights enhancements of slow wave Down Slope (left) and Negative peak Amplitude (right) in the same large fronto-parietal area showing higher SWA, which were both significantly increased in Night 2 compared to Night 1 (SnPM, $p < 0.05$).

memory of perceptual and motor skills (Diekelmann and Born, 2010), and several EEG studies have demonstrated that SWA is critically implicated in enhancing visuo-motor procedural learning (Huber et al., 2004a; Landsness et al., 2009; Maatta et al., 2010). In contrast, much less is known about the role of sleep in executive control and WM functions. A couple of studies employing the N-back task have shown that sleep can enhance WM memory performance in healthy individuals, including children and adults (Kuriyama et al., 2008; Zinke et al., 2018). Here, we found that an increase in SWA mediates these sleep-related improvements in the N back task. Our findings are consistent with another recent sleep EEG study, wherein a SWA increase was established after three weeks of WM training in children and adolescents (Pugin et al., 2015), and suggest that this increase can be observed more acutely (e.g., after three training sessions), and it is also present in the adult brain.

By performing hd-EEG recordings, we established that the SWA increase was localized on the right hemisphere and involved more prominently a large fronto-parietal region. Previous work has shown that SWA during sleep is locally regulated by daytime activities, such that learning a visuomotor adaptation task during the day leads to higher SWA over a parietal cortical area involved in rotation adaptation (Huber et al., 2004a; Hung et al., 2013). Similarly, extensive practice of audio-book listening and driving simulation tasks results in a local SWA increase in auditory and visuo-motor cortical areas, respectively (Hung et al., 2013). In the presents study, the SWA increase in fronto-parietal regions is consistent with functional neuroimaging data showing activation during N-back WM tasks in prefrontal, frontal and parietal cortical areas (Dima et al., 2014) as well as with a fronto-parietal SWA enhancement reported by another sleep hd-EEG study after an auditory N-Back task. Of note, in that study, the SWA increase was bilateral and more prominent on the left side, whereas we found the strongest effect was on the right fronto-parietal region. Possible explanations for this difference is that they employed an auditory N-back task, which is more likely to involve the language areas located on the left hemisphere (Pugin et al., 2015), and that they enrolled children and adolescents, groups in which lateralization has not fully developed. Furthermore, in a recent dynamic casual modeling of WM tasks in healthy, young adults it was reported that the level of right fronto-parietal activation was the best predictor of increasing memory load and task-related individual variability (Tononi and Cirelli, 2014), in line with our findings.

In addition to SWA, we investigated several slow wave parameters and found an increase in the down-slope and negative peak amplitude of those showing an overnight improvement in the 1 Back task. The slope of the slow wave changes as a function of synaptic strength, and it is considered a reliable measure of synaptic efficacy. Converging evidence from modeling, animal, and human electrophysiological data has shown that the slow wave slope is much steeper when synaptic strength is high

Table 4
Correlations between across night changes in Slow Wave Activity, Down-Slope, and Negative Peak Amplitude) and N 1-back in all participants and improvers only.

	N1-BACK PERFORMANCE (N2-N1) ALL SUBJECTS	N1-BACK PERFORMANCE (N2-N1) IMPROVERS ONLY
SWA in fronto-parietal cluster	$r = 0.48$; $p = 0.01$	$r = 0.75$; $p = 0.008$
SW DS in fronto-parietal cluster	$r = 0.41$; $p = 0.03$	$r = 0.56$; $p = 0.02$
SW NPA in fronto-parietal cluster	$r = 0.43$; $p = 0.03$	$r = 0.71$; $p = 0.01$

(e.g., early sleep) compared to conditions when it is low (e.g., late sleep). This effect is stronger for the down-slope, which is measured as the time derivate from the first zero crossing to the negative peak amplitude, relative to the up-slope, which is calculated from the negative peak amplitude to the second zero crossing (Esser et al., 2007; Riedner et al., 2007; Vyazovskiy et al., 2007). Here we found that the slow wave down-slope, but not the up-slope, was significantly increased in the 1 Back improvers. While the down-slope finding supports the notion that enhanced synaptic plasticity regulates WM performance, the absence of up-slope modulation may reflect a reduced sensitivity of this measure to synaptic strength, as reported above. Another intriguing possibility is that the lack of neuronal firing, reflected by the down-slope, rather than the resuming of neural activity, as captured by the up-slope, is primarily involved in modulating learning and memory during slow wave sleep (Tononi and Cirelli, 2014).

We also found a fronto-parietal increase in the slow wave negative peak amplitude. Large, high amplitude slow waves characterize the beginning of the night, and reflect a high-synaptic strength condition, wherein neurons exhibit frequent, fairly long periods of well-synchronized up and down states in the slow wave frequency range (0.8–1.2 Hz) (Bersagliere and Achermann, 2010). Thus, the fronto-parietal negative peak amplitude increases likely reflect higher synaptic activity occurring in those areas during the daytime. It also suggests that synaptic synchronization of local cortical neurons is an important mechanism implicated in ameliorating not only visuo-motor and perceptual procedural skills, but also higher cognitive functions such as WM.

The across night variations in SWA, down-slope, and negative peak amplitude were associated with next day performance changes in the 1 Back task. Significant correlations were present between each of these parameters and all study participants although, as expected, the strongest effects were observed in the 1 Back improvers. While several previous studies have shown that WM performance improves by training during wakefulness both in children and adults (Jaeggi et al., 2011; Li et al., 2008; Zinke et al., 2014), just a handful has investigated the effects of sleep on performance. Kuriyama and colleagues first showed in adults that sleep after daytime training leads to WM improvement when compared to post-training wakefulness (Kuriyama et al., 2008), and a recent EEG study showed a similar effect of sleep on the N back tasks in both adults and children, although the effect in the adult group was not as strong (Zinke et al., 2018). Another EEG study reported a fronto-parietal increase in sleep SWA following three weeks of WM training in children and adolescents, which positively correlated with their performance improvements (Pugin et al., 2015). Here, we showed that a similar increase in SWA is also present in adults, and that involves specific slow wave parameters, including down-slope and negative amplitude, which are more tightly linked to enhanced synaptic strength and efficacy. Furthermore, we established that these sleep-related beneficial effects do not require extensive practice but can be observed after just three training sessions.

An important implication of the present findings is that increasing slow wave parameters may ameliorate cognition, including higher cognitive functions like WM. In previous work our group, along with other research groups, has demonstrated that these parameters can be enhanced through a number of non-invasive interventions during sleep, including low-frequency (~1 Hz) Transcranial Magnetic Stimulation (Massimini et al., 2007), transcranial electrical stimulation (Marshall et al., 2004), olfactory (Perl et al., 2016), and auditory stimulation (Bellesi et al., 2014; Ngo et al., 2013). There is also evidence that some of these slow waves enhancing interventions benefit cognitive functioning (Marshall et al., 2004; Rihm et al., 2014). A recent meta-analysis reported that transcranial electrical stimulation during sleep can enhance declarative, but not procedural memory consolidation (Barham et al., 2016). Building on these promising findings, future studies should systematically assess the beneficial effects of increasing slow wave parameters on cognition, including WM and other domains of executive functions, especially in neuropsychiatric populations, such as patients with mild cognitive impairments, Alzheimer disease, schizophrenia, or PTSD, who commonly experience severe treatment refractory cognitive deficits. Similarly, the extent to which cognitive impairments resulting for acute and chronic sleep disturbances can be mitigated by slow wave sleep enhancement remains to be determined. In healthy sleepers, the extent to which slow wave sleep enhancement can also optimize learning and memory of recently acquired information can have significant benefits in several real-life situations (e.g., students studying for final exams, mitigation of cognitive decline in older adults, military personnel training for combat scenarios).

This study presents several limitations. First, we had a relatively small sample size (N = 25), which did not include women. Thus, these findings need to be replicated in larger groups of individuals, including women, to assess for possible heterogeneity and sex effects (Zinke et al., 2018). This is particularly relevant, given that it has been recently shown that gender has an impact on memory formation during a nap (Sattari et al., 2017). Second, although it extensively utilized as a WM paradigm, the N-back is thought not to represent an ideal measure of inter-individual differences in working memory (Jaeggi et al., 2010). Future studies employing distinct, specific cognitive tasks are therefore needed to fully establish the relationship between slow waves and specific domains of executive functions. Third, each participant performed all N back tasks. As such, it is possible that the a given subject was in the same group (i.e., improvers) across different tasks, which raises some concerns about non-independence. However, by selecting improvers and not improvers for each N back task, we maximized our chances to see whether slow wave activity changes were associated to task specific changes in performance. Furthermore, we found that there was a large overlap between groups, with 8 out of 11 improvers in the 1 Back task showing an overnight increase in 2 Back performance as well. Fourth, while we found an increase in slow wave parameters in the 1 Back improvers, this enhancement did not reach significance in the 2 Back group. One explanation for this negative finding is the relatively short training (three sessions) employed, which was insufficient to show a sleep effect for a more demanding task. Consistent with this interpretation, we found that 2 Back improvers had a smaller and more variable increase in performance compared to the 1 Back, and that they showed a similar, though smaller slow wave enhancement in the same fronto-parietal areas. Thus, in future work, the link between daytime training and sleep on improving cognitive performance should be systematically investigated. Finally, defining the trajectory and duration of the detected beneficial effects of increased slow wave sleep activity on WM over time remains to be established.

In conclusion, here we have demonstrated that higher slow wave activity in fronto-parietal regions predicts a better WM cognitive performance in healthy, young adults. In addition to providing novel evidence that slow waves are involved in ameliorating executive control and higher level cognitive abilities, above and beyond their established role in stabilizing procedural memories, the present findings show that these slow wave beneficial effects can occur in the adult brain and even after minimal training. This is especially relevant, when considering that WM and other executive function cognitive deficits are experienced by a variety of neuropsychiatric patients, and that preliminary evidence indicates that slow wave enhancing interventions can improve cognition, thus providing new insights and treatment strategies for those affected by those devastating brain disorders.

Disclosures

This was not an industry-supported study. The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Army or of the US Department of Defense (DoD). The authors completed this study without influence from the sponsors and report no competing interests. The authors do not have any conflicts of interest to disclose. This paper

has been approved for public release with unlimited distribution.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.02.020.

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