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Sleep spindles facilitate selective memory consolidation — Source link

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Abstract

Sleep has been shown to be critical for memory consolidation, and recent research has demonstrated that this consolidation effect is selective, with certain memories being prioritized for strengthening. Initial strength of a memory appears to be one metric the brain uses to prioritize memory traces for sleep-based consolidation, but the role of consolidation-mediating cortical oscillations, such as sleep spindles and slow oscillations, has not been explored. Here, N=54 participants studied pairs of words to three distinct encoding strengths, with recall being tested immediately following learning and again six hours later. N=36 had a two-hour afternoon nap opportunity following learning, whilst the remaining (n=18) remained awake throughout. Results showed a selective benefit of sleep on memory, with sleep preferentially consolidating weakly encoded items (p=.003). The magnitude of this effect (d=0.90, 95% CI=0.29-1.50) was similar when compared to a previous study examining the benefits of a full night of sleep (d=1.36, 95% CI=0.59-2.12). Within the nap group, consolidation of weakly encoded items was associated with sleep spindle density during slow wave sleep (r=.48, p=.003). This association was present when separately examining spindles coupled (r=.41, p=.013), and uncoupled (r=.44, p=.007) with slow oscillations. Memory was significantly better in individuals who showed an amount of slow oscillation-spindle coupling that was greater than what would be expected by chance (p=.006, d=1.15). These relationships were unique to weakly encoded items, with spindles not correlating with memory for intermediate or strong items. This suggests that sleep spindles facilitate selective memory consolidation, guided in part by memory strength.

Keywords

sleep, memory, consolidation, sleep spindles, slow oscillations, memory strength

Significance statement

Given the countless pieces of information we encode each day, how does the brain select which memories to commit to long-term storage? Sleep is known to aid in memory consolidation, but less research has examined which memories are prioritized to receive this benefit. Here, we found that compared to staying awake, sleep was associated with better memory for weakly encoded information. This suggests sleep helps to rescue weak memory traces from being forgotten. Sleep spindles, a hallmark oscillation of non-rapid eye movement sleep, mediates consolidation processes. We extended this to show that spindles selectively facilitated consolidation of weakly encoded memories. This provides new evidence for the selective nature of sleep-based consolidation and elucidates a physiological correlate of this preferential benefit.

Introduction

Sleep aids in the consolidation of memories (Stickgold, 2005; Klinzing et al., 2019). But consolidation is selective, with certain memories prioritized for retention over others (Payne et al., 2008; Diekelmann et al., 2009; Payne and Kensinger, 2010; Stickgold and Walker, 2013). It appears that certain salience cues present during the peri-encoding period can act as behavioral 'tags' that indicate which memories should be consolidated during sleep (e.g. Payne et al., 2008, 2012, 2015; Fischer and Born, 2009; Wilhelm et al., 2011; Payne and Kensinger, 2018). The initial strength of a memory appears to act as a sleep-based prioritization cue. Several studies have manipulated encoding strength by varying the number of item presentations given during encoding. Using this method, these studies suggest that *weaker* memories are prioritized for consolidation (Drosopoulos et al., 2007; Schapiro et al., 2017; Denis et al., 2019), although a minimum threshold does need to be met (Denis et al., 2019).

There is little work on the sleep correlates of this selective memory benefit. One study reported that the benefit of a nap for weakly encoded items was associated with both NREM and REM sleep, with NREM followed by a larger amounts of REM sleep being optimal for selective memory consolidation (Schapiro et al., 2017). The active systems consolidation theory of memory consolidation posits that during NREM sleep, especially slow wave sleep (SWS), memories in the hippocampus are repeatedly reactivated through the triple phase-locking of hippocampal sharp-wave ripples, thalamocortical sleep spindles, and neocortical slow oscillations (Rasch and Born, 2013). Specifically, de-polarizing slow oscillation upstates are thought to facilitate emergence of sleep spindles, which in turn mediate transfer of information reactivated during sharp wave ripples in the hippocampus, leading to long-term storage more dependent on neocortical sites (Klinzing et al., 2019). There is evidence for these oscillations, and especially their coupling, being involved in general memory consolidation processes (Niknazar et al., 2015; Latchoumane et al., 2017; Mikutta et al., 2019), but it is currently unknown if these oscillations act selectively based on the encoding strength of a memory.

When slow oscillation-spindle coupling events are detected, it is presumed to reflect the mechanistic process described above. However, some spindles are likely to 'co-occur' with slow oscillations by chance, based statistically on the number of detected slow oscillations, spindles, and overall sleep time. However, using intracranial recordings, coupling events have been shown to far exceed the number expected by chance (Staresina et al., 2015), suggesting these events reflect non-random, physiologically driven co-occurrences. We reasoned that if "causal", memory-based coupling exceeds chance levels, this non-chance coupling would be better at predicting memory performance than chance coupling. Because coupling probability has yet to be assessed in the context of memory effects, exploring this relationship was one of our goals here.

In a typical overnight design, the wake control group will learn information in the morning and be tested in the evening, whereas the sleep group learns in the evening and is tested the following morning. A nap design allows learning and test phases to occur at the same time of day for all participants, making the role of sleep clearer (Payne et al., 2009; Lo et al., 2014). It also restricts the amount of time spent awake that might expose participants to interfering information.

For these reasons, we used a daytime nap to investigate some of these unresolved questions. Participants spent the day in the sleep laboratory. In the morning, they learned word pairs to differing levels of encoding strength. Some participants then had a two-hour nap opportunity and were tested on their memory 4 hours later. Other participants remained awake in the lab throughout. We sought to understand 1) whether a nap prioritizes the consolidation of memories based on their encoding strength in a similar manner to a full night of sleep; and 2) whether sleep oscillations (namely sleep spindles and their coupling with slow oscillations) facilitate selective consolidation.

Methods

Participants

In total, 54 participants completed the full study protocol. The mean age of participants was 22 (SD = 3) years, and 76% were female. Participants reported no history of any sleep, neurological, or psychiatric disorders, normal bedtimes no later than 2am, and sleeping on average for at least six hours each night. For the three days prior to the study, participants were instructed to keep to a regular sleep schedule and abstain from caffeine on the morning of the study. Recruitment was through advertisements for a study of learning and memory placed on local college job boards. Participants received financial compensation for their time. The study received IRB approval from Beth Israel Deaconess Medical Center.

Design

The study design is depicted in **Figure 1**. All participants followed the same experimental procedure, except for whether they were allowed to take a nap (**Figure 1A**). After providing informed consent, participants filled out questionnaires about their sleep habits over the past three days, their general sleep quality over the past month (assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), and their current subjective sleepiness and alertness levels (Stanford Sleepiness Scale (SSS; Hoddes et al., 1972). Following this, participants were wired for EEG (see below). Then, they took part in the first experimental session. The session started with a 5-minute eyes-closed quiet rest session (all subsequent rest sessions were also 5 minutes eyes closed and will be analyzed in future studies of resting state activity; **Figure 1B**). They then studied pairs of words and were asked to try and visualize a scene containing the two objects described by the word pair (**Figure 1D**). After encoding, participants had a second quiet rest session, and then a cued recall test (immediate recall; **Figure 1E**), and finally a third rest period (**Figure 1B**). N = 36 participants were then given a 2-hour nap opportunity followed by four hours

spent awake in the lab watching TV. The remaining n = 18 participants were not given the opportunity to nap, so remained awake in the lab for six hours. These group sizes were similar to our previous publication that successfully found preferential consolidation of weakly encoded material (Denis et al., 2019). The nap group was oversampled due to our interests in sleep activity *within* this group. The second experimental session **Figure 1C**) occurred after the six-hour delay period. During this session, participants had a fourth quiet rest period, followed by a second cued recall test (delayed recall), and a fifth and final quiet rest session. Finally, at the very end of the protocol, participants filled out two additional questionnaires assessing trait abilities in forming internal visualizations [measured using the vividness of visual imagery questionnaire (VVIQ; Marks, 1973) and the visual portion of the Plymouth sensory imagery questionnaire (PSIQ; Andrade et al., 2014)].

Encoding

During the encoding task, participants studied 180 pairs of words. Participants were instructed, for each trial, to try to visualize a scene containing the two objects in the word pair (*e.g.,* "blanket – wheel"). Word pairs were assigned to either a weak (n = 60), intermediate (n = 60), or strong (n = 60) encoding condition, with assignments randomized across participants. Word pairs in the weak condition were presented once (n = 60 trials), pairs in the intermediate condition twice (n = 120 trials), and those in the strong condition four times (n = 240 trials), for a total of 420 trials. In a prior study, we demonstrated that this procedure produces distinct levels of encoding strength (Denis et al., 2019). The order of presentation was pseudorandomized for each participant, with at least two trials separating multiple presentations of any one item.

On each trial (**Figure 1D**), a fixation cross appeared in the center of the screen for 2,000-3,000ms, followed by the word pair for 2,000ms. This was followed by a blank screen for 500ms-1,000ms. Participants were then asked whether they had visualized a scene containing both objects,

responding (either yes or no) by a keypress. After responding, a blank screen appeared for 1,000ms, and then the next trial began. After every 70 trials, there was a break lasting a minimum of one minute and terminated by the participant. The variation in presentation times for the fixation cross and blank screen was to facilitate future event-related EEG analyses on the encoding data, with the jitter allowing for the best assessment of memory encoding activity, rather than preparatory responses to the stimuli.

Recall

Both the immediate and delayed recall tests followed the same procedure (**Figure 1E**). Each trial began with a fixation cross on the screen for 2,000ms-3,000ms. Then, the first word of the pair appeared for 2,000ms. During this period, participants were instructed to recall the second word of the pair, but not to type it. After 2000-2500ms, a box appeared under the first word, indicating participants could enter their answer. This approach allowed for time-locked analysis of memory recall in future analyses. A separate study (n = 52) confirmed that variable presentation times in this window did not impact immediate memory performance (not reported). Participants were instructed to respond as quickly and as accurately as possible, and that there was no penalty for guessing. If no response was entered after seven seconds, a prompt appeared telling participants to respond, and if the participant had not begun typing a response after a further three seconds, the program advanced to the next trial. Each word pair was tested once, for a total of 180 trials. Order of presentation of the word pairs was randomized for each session and for each participant. At the end of the immediate recall session, participants were told that their memory for the word pairs would be tested again at the end of the day. All tasks were administered using custom scripts written in the Psychtoolbox package for MATLAB (Kleiner et al., 2007).

EEG acquisition and preprocessing

EEG was collected from all participants throughout the protocol. During the delay period, participants remained connected to the EEG equipment, but no data were acquired. Only EEG data recorded during the nap is reported here. Data were acquired from 57 EEG channels, with electrodes positioned in accordance with the 10-20 system. Additionally, electrodes were placed on the left and right mastoids, above the right eye and below the left eye (for EOG measurements), two placed on the chin (for EMG measurements), one on the forehead (recording reference) and one on the collarbone (ground). An Aura-LTM64 amplifier and TWin software were used for data acquisition (Grass Technologies, Warwick, RI). All impedances were kept below 25 KOhm. The sampling rate was 400Hz.

Sleep scoring was performed according to standard criteria (Iber et al., 2007). Sleep scoring and subsequent sleep statistic generation was performed in MATLAB (The Mathworks, Natick, MA). EEG analyses were performed on the full high-density EEG array using custom MATLAB scripts. First, all EEG channels were re-referenced to the average of the two mastoids, band-pass filtered between 0.3 - 35Hz and notch filtered at 60Hz. Data was then artifact rejected based on visual inspection of each 30-second epoch. Bad epochs were marked and removed from subsequent analyses, and bad channels were marked and interpolated using a spherical splines algorithm implemented in EEGLAB (Delorme and Makeig, 2004). All artifact-free data were then subjected to further analysis.

Sleep spindle detection

Spindles were automatically detected at every electrode during stage 2 and SWS using a modification of a previously validated wavelet-based detector (Wamsley et al., 2012). In brief, the raw EEG signal was subjected to a time-frequency transformation using complex Morlet wavelets. Spindles were detected on each channel by applying a thresholding algorithm to the extracted wavelet scale in the range

corresponding approximately to 12 - 15Hz (center frequency 13.5Hz). A spindle was detected whenever the wavelet signal exceeded a threshold of 9 times the median signal amplitude (as opposed to 4.5 times the mean in the original algorithm) of all artifact-free epochs for a minimum of 400 milliseconds (Mylonas et al., 2019). Our main metric of focus was spindle density (spindles per minute) in NREM sleep (stage 2 and SWS) based on previous work showing correlations between spindle density and declarative memory consolidation (Gais et al., 2002; Cox et al., 2012).

Slow oscillation detection

Slow oscillations were detected at every electrode using a second automated algorithm that band-pass filtered the EEG between 0.5 and 4Hz and identified all positive-to-negative zero crossings. Candidate slow oscillations were marked if two such consecutive zero crossings fell 0.5 – 2.0 seconds apart. Peak-to-peak amplitudes for all candidate slow oscillations were determined, and oscillations in the top quartile (*i.e.*, with the highest amplitudes) at each electrode were retained as slow oscillations. The use of this cutoff has been used in previous research (Staresina et al., 2015; Helfrich et al., 2018).

Slow oscillation-spindle coupling

Slow oscillation-spindle couplings were identified for every electrode. First, EEG data was band-pass filtered in the delta (0.5 - 4Hz) and sigma (12 - 15Hz) bands. Then, the Hilbert transform was applied to extract the instantaneous phase of the delta-filtered signal and instantaneous amplitude of the sigma-filtered signal. For each detected spindle, the peak amplitude of that spindle was determined. It was then determined whether the spindle peak occurred within the time course of any detected slow oscillation. If the spindle peak was found to occur during a slow oscillation, the phase angle of the slow oscillation at the peak of spindle was determined. Finally, for each electrode on each participant, we extracted the percentage of all spindles that were coupled with slow oscillations, the coupled and uncoupled spindle

densities, and the average coupling phase angle for all coupled spindles. Coupling strength was assessed as the mean vector length, though this metric should be interpreted with caution as it is known to be biased when the number of coupled events is low.

To better assess whether coupling results reflect a "true" co-occurrence of the two oscillations, we needed to ensure that the number of coupling events exceeded what would be expected by chance, given the number of detected slow oscillations, sleep spindles, and time spent in SWS (Staresina et al., 2015). To this end, the observed signal was compared to a randomized signal where the spindle signal was circularly shifted, and coupling was recalculated. This was performed over 1,000 iterations to generate a null distribution of slow oscillation-spindle coupling. The null distribution was then compared to the observed values. Across each participant/electrode, we calculated the percentage of participants and electrodes where the degree of coupling was significantly higher ($p < .05$) than what would be expected by chance (Staresina et al., 2015).

Spectral power

The power spectrum on every channel for all artifact-free stage 2 and SWS epochs was calculated. To counter the typical 1/f scaling of the power spectrum, power was derived for the temporal derivative of the time series (Cox et al., 2017). Power spectral density (PSD) was estimated for each epoch using Welch's method (pwelch function in MATLAB) with 5 second windows and 50% window overlap.

Statistical analysis

Behavioral results were assessed using repeated measures ANOVAs, with *post hoc* t-tests where applicable. For analysis of visualized items, an item was considered visualized if the participant reported making a visualization on at least one of its presentations. Change in memory across sessions was

calculated as the relative change in recall [(delayed recall - immediate recall) / immediate recall]. correlations. Behavioral and sleep stage correlation analyses were performed in R.

To take advantage of the high-density EEG array, and control for multiple comparisons across electrodes, correlations between sleep oscillatory EEG measures and change in memory were performed using a cluster-based permutation approach in the FieldTrip toolbox for MATLAB, using the *ft_statfun_correlationT* function (Oostenveld et al., 2011). Separate analyses were performed for sleep spindles, slow oscillations, slow oscillation-spindle coupling, and spectral power in the delta and sigma bands. All analyses used the following parameters: 10,000 iterations; a *clusteralpha* of 0.05 with the default *maxsum* method to determine cluster significance; and a significant threshold of 0.05. For comparisons between spindle properties in stage 2 and SWS, the same procedure was followed except the *ft_statfun_depsamplesT* function was used.

Correlations between coupling phase angles and memory were performed using circular-linear correlations, implemented in the CircStat toolbox for MATLAB (Berens, 2009). As circular-linear correlations are not implemented in the FieldTrip environment, the false-discovery rate (FDR) was used to control for multiple comparisons. Comparisons of correlation coefficient magnitudes were performed using Meng's Z test (Meng et al., 1992; Spaak, 2020).

Results

Behavior

We first examined visualization performance during memory encoding (**Figure 2A**). As the number of item presentations increased, so did the number of word pairs successfully visualized (F (2, 104) = 64.7, p < .001, ηp^2 = .77). All follow-up pairwise comparisons were highly significant (all t (53) > 6.1, all p <

.001, $d > 0.47$). This is not surprising, given that a word pair was considered visualized if it was reported to have been successfully visualized on at least one of its presentations. Overall, participants were highly successful at visualizing the word pairs, with 78% of the word pairs that were seen just once being reported as successfully visualized in a scene containing the two objects. Whilst additional presentations did confer a significant benefit on the percentage of items visualized, these effects were relatively modest (2 PRES - 1 PRES = 11%, 4 PRES - 2 PRES = 7%). Importantly, there was no difference between the Wake and Sleep groups in the percentage of word pairs successfully visualized (F (1, 52) < 0.01, p = .99, ηp^2 < .001), nor was there a significant interaction between presentation number and group (F (2, 104) = 0.2, p = .86, ηp^2 = .003).

Even though the increase in percentage of items visualized as presentation number increased was of a similar magnitude to our previous report, the overall number of visualized items was far greater in the present study (Denis et al., 2019). Indeed, after four presentations, participants reported successfully visualizing almost all (96%) of the word pairs. We were therefore unable to look at differences in recall and consolidation between successfully and unsuccessfully visualized items, due to a lack of sufficient not-visualized trials. As such, all subsequent analyses report on all trials together.

We next looked at immediate recall accuracy to confirm that the presentation number manipulation successfully induced different levels of encoding strength (**Figure 2B**). There was a significant main effect of presentation number on immediate recall performance (F (2, 104) = 163, p < .001, ηp^2 = .75), with significant increases in the percentage of word pairs recalled as the number of presentations during encoding increased (1 PRES vs 2 PRES = 26% increase, 1 PRES vs 4 PRES = 47% increase, 2 PRES vs 4 PRES = 21% increase; all t (53) > 7.7, p < .001, d > 0.90). There were no differences between groups (F (1, 52) < 0.01, p = .97, ηp^2 < .001), and there was no interaction between presentation number and group (F (2, 104) = 1.04, p = .36, ηp^2 = .01). These results show that the items

were encoded at three distinct strengths, and that learning was equivalent between the nap and wake groups.

We then looked at the effects of the nap on memory at re-test 6 hours later. We calculated the relative change in recall at the delayed test compared to the immediate test (**Figure 2C**). There was a significant main effect of group (F (1, 52) = 6.24, p = .02, ηp^2 = .061), with the nap group showing overall less forgetting than the wake group (t (52) = 2.02, p = .048, d = 0.58). This suggests that across all items, sleep benefitted memory. There was no main effect of presentation number (F (2, 104) = 0.89, p = .41, ηp^2 = .017). There was, however, an interaction between presentation number and group (F (2, 104) = 3.2, p = .047, ηp^2 = .057), suggesting that the benefit of sleep on memory differed depending on encoding strength. Follow-up t-tests comparing relative change in recall between groups at each level of presentation number revealed a significant difference for 1 PRES items, with significantly more forgetting in the wake group (13%) compared to the nap group (2%; t (52) = 3.12, p = .003, d = 0.90). For both the 2 PRES and the 4 PRES conditions, group differences were not significant (2 PRES, t (52) = 0.98, p = .33, d = 0.28; 4 PRES, t (52) = 0.02, p = .98, d = 0.01). Within the nap group, there was no difference in the amount of forgetting between presentation number conditions (all t (35) < 1.17, p > .24, d > 0.15), but within the wake group, there was significantly more forgetting of 1 PRES items than of 4 PRES items (t (17) = 2.24, p = .039, d = 0.90), with no significant difference between 1 PRES and 2 PRES (t (17) = 1.70, p = .11, d = 0.32) or 2 PRES and 4 PRES items (t (17) = 1.09, p = .29, d = 0.47).

Finally, we investigated whether the magnitude of the selective memory consolidation effect differed between a nap and a full night of sleep. The sleep-wake group difference for relative change in recall was largest for a 12-hour overnight delay period (d = 1.36, 95% CI = [0.59, 2.12]), followed by the 6-hour daytime delay (d = 0.90, 95% CI = [0.29, 1.50]), with a 24 hour delay (overnight plus a daytime wake) showing the smallest effect (d = 0.76, 95% CI = [0.06, 1.46]). Given the overlap of confidence

intervals, this suggests the effect of sleep on the consolidation of 1 PRES items is similar across a nap and a full night of sleep.

The behavioral results show that a 2-hour nap opportunity significantly reduced forgetting over a 6-hour retention interval compared to staying awake. Furthermore, this benefit was selective. Over a period spent awake, items that were weakly encoded were forgotten at a higher rate than items that were more strongly encoded. After sleep, however, weakly encoded items showed similar retention to more strongly encoded information.

Sleep architecture and sleep stage correlations

We next investigated the sleep physiology correlates of this selective sleep-dependent consolidation effect. Sleep statistics are presented in **Table 1**. There were no significant correlations between change in memory (for either all items or any of the three encoding strengths) and time or percentage of the nap spent in any sleep stage (stage 2, SWS, stage 2 + SWS, REM; **Supplementary Table 1**)

Sleep spindles

To look at associations between sleep spindles and selective memory consolidation, we first examined sleep spindle density across all NREM (stage 2 and SWS) sleep. Topography of NREM detected sleep spindle density is shown in **Figure 3A**. We then calculated scalp-wide correlation coefficients between spindle density and relative change in recall, shown in **Figure 3B-E**. We did not observe any significant correlations between spindle density and relative change in recall across all items. But when broken down by number of presentations, significant correlations were observed between spindle density and change in memory for 1 PRES items across 22 fronto-central electrode sites (cluster $t_{sum} = 49.89$, $p = .044$), with an average within-cluster correlation coefficient of $r = .38$.

This association was unique to 1 PRES items, with no significant correlations found between spindle density and change in memory for 2 PRES or 4 PRES items. The magnitude of the spindle density - 1 PRES correlation was trending towards being significantly larger than the average coefficient of the same 22 electrodes for the 2 PRES (r = .01) and 4 PRES (r = .02) conditions (1 PRES vs 2 PRES p = .066; 1 PRES vs 4 PRES p = .053).

Next, we looked at whether the correlation between spindle density and 1 PRES memory consolidation was driven primarily by spindles in stage 2 sleep or SWS (**Figure 4**). Topography of spindle density in stage 2 and SWS are shown in **Figure 4A&B** respectively. Although spindle density was numerically higher in stage 2 compared to SWS, the differences were not large, with only a trend for a significant difference at 6 left temporal electrodes (t_{sum} = 16.13, p = .088; **Supplementary Figure 1A**) and stage 2 and SWS spindle densities were highly correlated at all electrodes (all p < .001 FDR adjusted; **Supplementary Figure 1B**). Whereas stage 2 spindle density appeared maximal at frontal sites, maximal SWS spindle density extended more centro-parietally. The association between spindle density and 1 PRES items was driven by SWS spindle density. Whereas no significant correlations were found between stage 2 spindle density and 1 PRES consolidation (**Figure 4C**), we found a large, widespread cluster of significant correlations for SWS spindle density (37 electrodes, cluster t_{sum} = 113.2, p = .01; **Figure 4D**). When directly comparing the average correlation coefficients across electrodes, the difference in r values between SWS (r = .48) and stage 2 (r = .28) was significant (p = .037). Given our specific predictions and the robust links reported in the existing literature (Gais et al., 2002; Cox et al., 2012) we focused on relationships between memory and spindle density. However, additional spindle properties (amplitude, duration, and frequency) were explored and are reported in **Supplementary Figure 2**.

The relationship between SWS spindles and memory was strongest for 1PRES items. When comparing correlation coefficients between spindles and 1PRES, 2PRES, and 4PRES items, the spindle-1PRES correlation (r = .55, p < .001) was significantly larger than the 2PRES (r = .15, p = .038) and 4

PRES (r = .051, p = .008) correlations (at electrode Fz; see **Supplementary Figure 3** for scalp maps). The correlations between spindles and 2PRES and 4PRES memory were not significantly different in magnitude (p = .30).

Slow oscillation-spindle coupling

A key tenet of the active systems consolidation theory is that memories are reactivated and thus consolidated through the precise coupling of hippocampal sharp-wave ripples, thalamocortical sleep spindles, and cortical slow oscillations. A number of previous studies have indicated that slow oscillation-spindle coupling at the scalp EEG level is correlated with memory consolidation. Here we investigated slow oscillation-spindle coupling in SWS, and its relation to the selective consolidation of weakly encoded information.

Across the whole scalp, M = 17% (SD = 2%) of SWS spindles co-occurred with slow oscillations (**Figure 5A**). The topography showed slightly higher % coupling at frontal regions. The topography of coupled and uncoupled spindle density are shown in **Figure 5B** and **Figure 5C,** respectively. Uncoupled spindle density was significantly higher than coupled spindle density across the scalp (all 57 electrodes, p < .001 FDR adjusted). The distribution of uncoupled spindles across the scalp was highly similar to that of all spindles, as seen in **Figure 4B**. Coupled spindles on the other hand showed a more restricted distribution, with the highest density appearing in frontal regions.

The density of coupled spindles was highly correlated with overall spindle density and uncoupled spindle density across the scalp (**Supplementary Figure 4**). Averaging across all electrodes, 64% of participants showed levels of coupling significantly higher than would be expected by chance. This percentage was higher in frontal regions, and lower in posterior regions(**Figure 5D**).

We then asked whether coupled spindles were more strongly correlated with memory consolidation than uncoupled spindles. Both coupled (**Figure 5E**) and uncoupled (**Figure 5F**) SWS spindle density significantly correlated with the consolidation of weakly encoded items. For uncoupled spindles, the significant cluster encompassed the same 37 fronto-central electrodes as the overall spindle density analysis; cluster t_{sum} = 107.3 , p = .01. On the other hand, a smaller cluster of correlations was observed for coupled spindle density over right frontal regions (19 electrodes, t_{sum} = 49.7, p = .029; **Figure 5E**). Across significant electrodes, the correlations with memory were not significantly different between all SWS spindles (r = .48), uncoupled SWS spindles (r = .44), and coupled SWS spindles (r = .41); all difference in magnitude comparisons = p > .61. When both coupled and uncoupled spindle density were entered as separate predictors in a multiple regression model, neither predicted memory independently of the other (coupled spindles: β [95% CI] = 8.46 [-10.98, 27.91], p = .38; uncoupled spindles: β [95% CI] = 3.90 [-1.77, 9.56], p = .17).

To better understand why coupled spindles did not confer a significantly greater memory benefit than uncoupled spindles we divided the group into those who showed levels of coupling which *exceeded* the amount expected by chance and those whose coupling levels did not exceed chance. Participants whose coupling exceeded chance levels showed significantly better consolidation of 1PRES items compared to participants whose coupling was not greater than chance (t (34) = 2.91, p = .006, d = 1.15; **Figure 6A**). This effect remained when spindle density was controlled for in an ANCOVA model (main effect of group, controlling for spindle density: F (1, 33) = 9.38, p = .004, ηp^2 = .22).

If the coupling in those who did not show above chance levels were randomly distributed, it would be expected that the phase distribution of these participants would also be random. This was not the case. The average coupling angle (t (34) = 0.76, p = .45, d = 0.28) and coupling consistency (t (34) = -0.59, p = .56, d = 0.21) were comparable between the two groups (**Figure 6B**). This suggests that spindles coupled to a preferred phase of the slow oscillation regardless of whether the overall number of couplings

was greater than expected by chance or not. Finally, we asked whether "corrected" coupling density (observed coupling – expected random coupling) would predict memory. Although we found a positive relationship with this measure, it was not significant (r = .25, p = .14; **Figure 6C**). There were no differences between the groups in terms of overall number of spindles, slow oscillations, or time spent in SWS sleep (all p > .28).

It appeared that only the densities of coupled and uncoupled spindles were important to memory consolidation. Neither the overall percentage of spindles coupled with slow oscillations, nor the specific phase angle of the coupling, showed any significant relationships with memory for prioritized items (**Supplementary Figure 5**).

Slow oscillations and spectral power

Having shown that SWS sleep spindles correlated with consolidation of weakly encoded information, we next wanted to investigate whether this relationship was unique to sleep spindles. We focused on slow oscillation density and amplitude, plus spectral power in the Delta (1-4Hz) and Sigma (12-15Hz) bands. We looked specifically at SWS sleep and 1 PRES memory consolidation. We did not find any significant correlations between any of these measures and selective memory consolidation (**Supplementary Figure 6**).

Subjective sleep measures

Subjective sleep variables are shown in **Table 2**. At the start of the second session, the sleep group reported feeling significantly more refreshed than the wake group (t (52) = 2.12, p = .039, d = 0.61). However, the change in recall between the second and first session (the key dependent variable of this study) was not associated with subjective feeling of being refreshed at the second session in either group

(sleep: $r = .13$, $p = .45$; wake: $r = .05$, $p = .84$) There were no other differences between the groups on any other of the subjective measures.

Discussion

Here, we set out to investigate whether a nap selectively consolidates memories based on their initial encoding strength in the same manner as does a full night of sleep, and what the sleep EEG oscillatory correlates of selective memory consolidation are. With regards to the first aim, we found a selective benefit of sleep-dependent memory consolidation for items that were relatively weakly encoded. This pattern of results is similar to our previous study that utilized 12- and 24-hour delay periods before retesting (Denis et al., 2019), a finding also seen by other groups (Drosopoulos et al., 2007; Schapiro et al., 2017). The results of the present study suggest that selective consolidation can also be seen after a 6-hour delay containing a two hour nap.

In our previous study, we found that weakly encoded items (manipulated by the number of exposures) were only consolidated when the items had been successfully visualized during encoding. We were unable to investigate this directly in the present study, as participants reported being able to visualize a far larger percentage of items than in that study. This study used a 2,000ms presentation time, compared to 1,500ms previously (Denis et al., 2019). The most likely explanation is that this 500ms increase in presentation time was enough to make it more likely that the word pair would be visualized. Although we were unable to perform analyses directly comparing visualized to not-visualized word pairs, given that 88% of items were visualized, our behavioral results primarily reflect encoding with successful visualization.

As encoding strength increased, the benefit of sleep disappeared. Over a period of wake, the weakly encoded information fades from memory faster than more strongly encoded material. Across sleep

however, it appears that those items that would have faded from memory across wake are "rescued" from this fate, such that forgetting is no greater for weakly than strongly encoded word pairs. It is interesting to consider why the brain would want to rescue these memories. Other research has shown that memories of high future utility, and high emotional valence, are prioritized for sleep-dependent consolidation (Payne et al., 2008, 2015; van Dongen et al., 2012) In both of these cases, it may be assumed that the prioritized memories were stronger memories. How can this be reconciled with the finding in our studies that weaker memories are prioritized?

Little is known about the hierarchy of salience cues tags in terms of which sleep will act upon. For instance, in a case where there is a mixture of emotional memories, highly rewarding memories, and weakly encoded but otherwise neutral memories, the emotional and highly rewarding memories may take precedence over the weakly encoded but unemotional and unrewarding items. In this sense, being weakly encoded may be low in the hierarchy, and only be consolidated after other information with more "important" tags has been consolidated. Relatedly, a number of studies have implicated REM sleep in emotional memory consolidation (Nishida et al., 2009; van der Helm et al., 2011; Groch et al., 2013; Kim et al., 2019). Our findings on initial encoding strength imply NREM processes, suggesting that different prioritization tags or tags on different types of memories may be read during different stages of sleep. To further understand the nature of this hierarchy, future research should systematically compare the interactions between different salience cues, and better understand the neural markers that constitute the behavioral tags (e.g. Cunningham et al., 2014; Bennion et al., 2016; Alger et al., 2019).

We did not find the amount of time spent in any particular sleep stage associated with memory consolidation, although earlier studies have found correlations between word-pair consolidation and SWS (Plihal and Born, 1997). But we did find that sleep spindles, particularly during SWS, correlated with the selective consolidation of weakly encoded information. This fits with previous work showing that consolidation of declarative memories is most closely associated with SWS spindles (Cox et al., 2012).

Spindles are involved in memory reactivation processes and are believed to function mechanistically by inducing plasticity in learning-related regions (Fogel and Smith, 2011; Fernandez and Luthi, 2019). The fact that spindles showed the largest association to weak item consolidation compared items with stronger encoding suggests that spindles are less effective in enhancing more strongly encoded information. Within the active systems consolidation hypothesis, our findings argue that during sleep weakly encoded memories were selectively reactivated in order to strengthen them, and spindles facilitated this process. Studies investigating different prioritization cues; namely future utility (Wilhelm et al., 2011; Studte et al., 2017) and directed forgetting (Saletin et al., 2011; Alger et al., 2019) have similarly found that sleep spindles act selectively. These findings, taken together with the results reported here, represent evidence for an emerging hypothesis that sleep spindles are involved in selective memory consolidation based on encoding-related salience tags.

The active systems consolidation hypothesis specifically emphasizes the importance of coupling between key cortical and subcortical oscillations, and indeed a number of prior studies have shown the degree of coupling to be associated with sleep-dependent consolidation (Mölle et al., 2009; Niknazar et al., 2015; Demanuele et al., 2016; Muehlroth et al., 2019). However, we found that both coupled and uncoupled sleep spindles correlated with memory consolidation of weakly encoded items, with the magnitude of their associations being almost identical. When coupled and uncoupled spindle densities were entered as separate predictors in a multiple regression, neither were significant independent predictors of memory. This is likely due to the extremely high correlation between coupled and uncoupled spindles, such that neither significantly predicts memory *independently* of the other.

Recent work has noted the importance of identifying “true” or "causal" co-occurring events, by investigating whether observed coupling differs from what would be expected by chance (Staresina et al., 2015). Applying this idea to the data reported here, we found significantly better memory of weakly encoded information in participants who showed significantly more coupling events than would be

expected by chance, compared to participants whose coupling was no different from chance. This suggests that coupling is only beneficial when the number of events is greater than what would be expected based on chance alone.

Whilst intriguing, this observation needs further work to be fully understood. For instance, we did not find any differences in coupling timing or consistency between these two groups. This suggests that coupling occurred at a preferential phase angle regardless of whether number of events exceeded chances. It is possible that in individuals where coupling did not exceed chance, levels of cortical activation required to induce a spindle did not occur as frequently. It is also possible that in these participants, memory consolidation was poorer because their sleep prioritized other functions (e.g., restoration; Plante et al., 2016) over memory functions. Future studies manipulating degree of sleep debt, as well as comparing differences in coupling probability between baseline and learning sleep periods are needed to fully explore these possibilities. In addition, the properties of coupling *across* a night of sleep have yet to be explored. Giving the multiple functions of sleep, it would be interesting to ask whether coupling during the early, SWS rich periods, are significantly different from late night SWS, where overall slow oscillation amplitudes are lower (Jaramillo et al., 2020). In general, these results emphasize the importance of solidifying our understanding of what gives rise to spindle coupling events, and how they relate to subcortical activity such as hippocampal sharp-wave ripples (Coon et al., 2019)

Our results suggest that spindles are uniquely involved in selective consolidation processes, as we did not find any correlations between consolidation of prioritized memories and either slow oscillations in isolation or spectral power in either the delta or sigma bands. Computational models have suggested different roles of sleep spindles and slow oscillations in memory consolidation. In particular it has been suggested that slow oscillations may prevent consolidation of weak memories, leading to forgetting of the weak memories unless sleep spindles precede the slow oscillations (Wei et al., 2018). This interesting observation should be followed up by more experimental work designed to unpack the interplay between

selective consolidation of memories and the myriad of sleep oscillatory features believed to benefit memory.

How the brain selects memories to be consolidated during sleep is a critical question in efforts to further our understanding of the memory functions carried out by sleep. Here, we add to the literature by suggesting that one of these selection mechanisms is initial encoding strength, and that the brain preferentially consolidates weaker memory traces across sleep, when all else is equal. We also provide evidence, for the first time, that sleep spindles specifically facilitate this selective consolidation. This fits with other research showing that prioritized memories are correlated with subsequent spindle activity. Future work now needs to address how prioritization tags may interact with each other, as well as understanding the neural basis of the mechanisms that govern sleep-dependent memory consolidation.

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Table 1. Sleep statistics

	Mean	SD
Total sleep time (min)	94.5	23.7
Sleep onset latency (min)	10	6.9
Wake after sleep onset (min)	12.2	18.1
Sleep efficiency (%)	79.5	17.1
Stage 1 time (min)	4.7	2.9
Stage 2 time (min)	48.5	17.1
SWS time (min)	21.6	14.4
REM time (min)	19.8	12.9
Movement time (min)	1.7	1.8
Stage 1 percentage (%)	5.1	4.0
Stage 2 percentage (%)	52.2	14.3
SWS percentage (%)	22.4	13.5
REM percentage (%)	20.2	12.1
Movement percentage (%)	1.9	2.1

Note. SD = Standard deviation. SWS = Slow wave sleep, REM = Rapid eye movement

Table 2. Subjective sleep variables

	Sleep M (SD)	Wake M (SD)	sig	d
PSQI global score	4.6 (2.6)	4.3 (2.7)	.64	0.14
3-night log sleep onset (min)	16.8 (9.7)	18.7 (18.2)	.63	0.14
3-night log hours asleep	7.4 (0.8)	7.7 (0.7)	.13	0.44
3-night log sleep quality	1.86 (0.54)	1.96 (0.48)	.50	0.20
Session 1: Concentration	73.4 (17.2)	67.7 (21.4)	.30	0.30
Session 1: Refreshed	63.1 (24.5)	52.4 (23.8)	.13	0.44
Session 1: Sleepiness	2.53 (0.74)	2.50 (0.99)	.91	0.03
Session 2: Concentration	79.9 (14.4)	73.4 (19.7)	.18	0.40
Session 2: Refreshed	75.4 (20.4)	61.7 (25.8)	.039	0.61
Session 2: Sleepiness	2.0 (0.83)	2.3 (1.03)	.21	0.37

Note. Sig = *p* value for between-groups t-test. PSQI = Pittsburgh sleep quality index (theoretical range = 0-21, a higher score = worse sleep quality). 3-night sleep log quality theoretical range = 1 - 4, a higher score = worse sleep quality. Concentration and refreshed items theoretical range = 0 - 100, a higher score = better concentration / more refreshed. Sleepiness item theoretical range = 1-8, a higher score = greater subjective sleepiness.

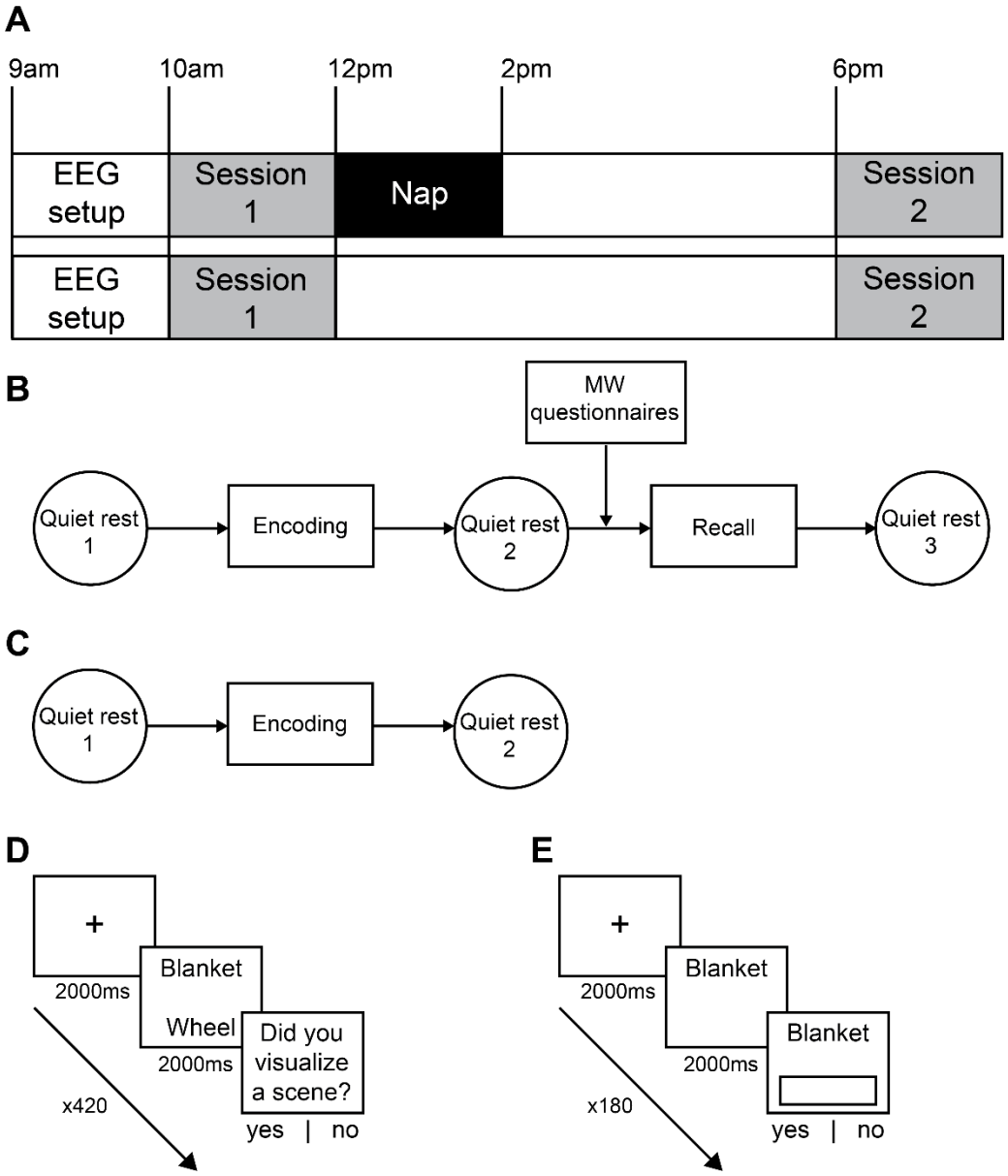

Figure 1 - Study timeline. **A -** Timeline of the protocol. **B** - During Session 1, participants completed a 5-minute rest period followed by the encoding task (**D**), and a second 5-minute rest session. They then performed a cued recall test (immediate recall; **E**), followed by a final quiet rest session. **C**- Session 2 began with a fourth quiet rest, followed by a second cued recall (delayed recall; **E**), and a fifth quiet rest. **D** - Encoding. Each encoding trial began with a fixation cross that appeared on the screen for 2000-3000ms, followed by the word pair for 2000ms. After the presentation of each word pair, participants were asked if they had been able to successfully visualize a scene containing the two word-pair objects. A total of 180 word pairs were displayed, with 60 being viewed 1 time, 60 being viewed 2 times, and 60 being viewed 4 times, for a total of 420 trials. **E** - Recall. Both the immediate and delayed recall session followed the same procedure. First, a fixation cross appeared for 2000-3000ms. Then, the first word of the pair appeared alone for 2000-2200ms. During this window, participants were instructed to think as hard

as possible about what the correct second word was. Then, a box appeared underneath the first word, indicating that they could start typing in their answer. There were a total of 180 recall trials.

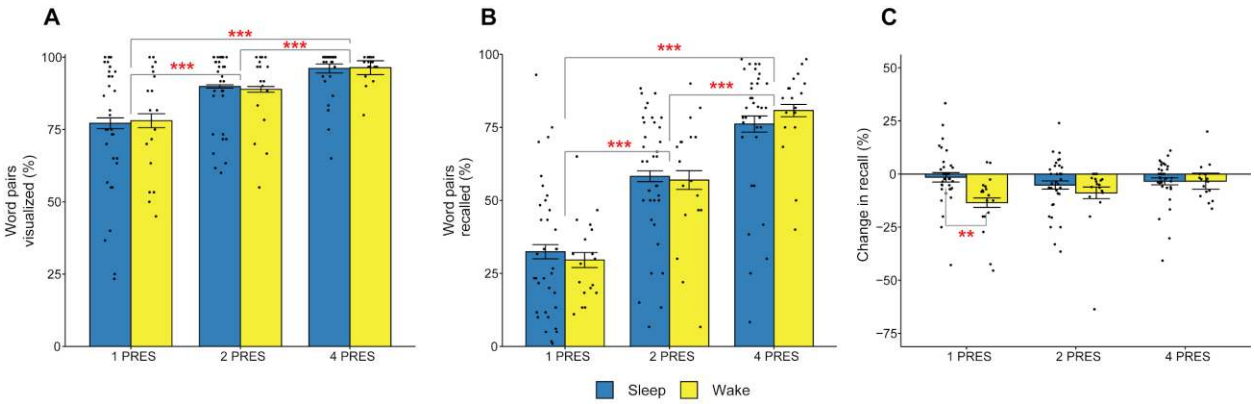

Figure 2. Behavior**. A** - Percentage of word pairs visualized during encoding. **B** - Percentage of word pairs recalled during immediate recall. **C** - Relative change in the percentage of word pairs recalled between delayed and immediate recall. Error bars display the standard error. "*n* PRES": word pairs presented *n* times. *** = $p < .001$, ** = $p < .01$

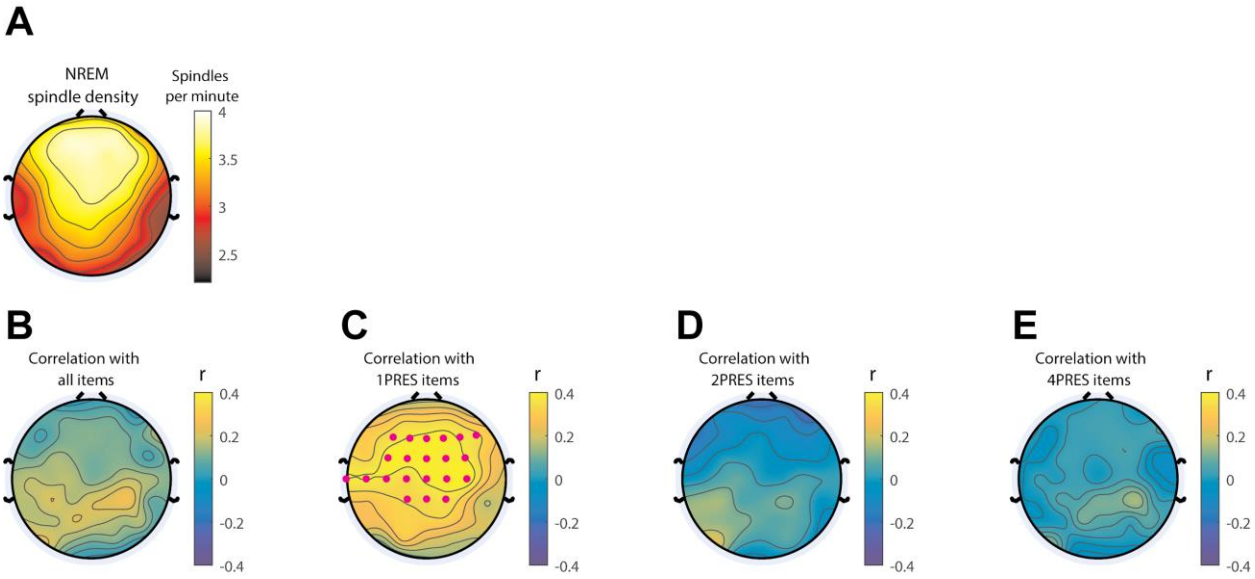

Figure 3. Spindles during NREM sleep. **A** - Spindle density (spindles/min) across all stage 2 and SWS. **B** - Correlations between spindle density and change in recall for all items. **C** - Correlations between spindle density and change in recall for 1 PRES items. **D** - Correlations between spindle density and change in recall for 2 PRES items. **E** - Correlations between spindle density and change in recall for 4 PRES items. Electrodes with significant correlations following cluster correction indicated with red dots.

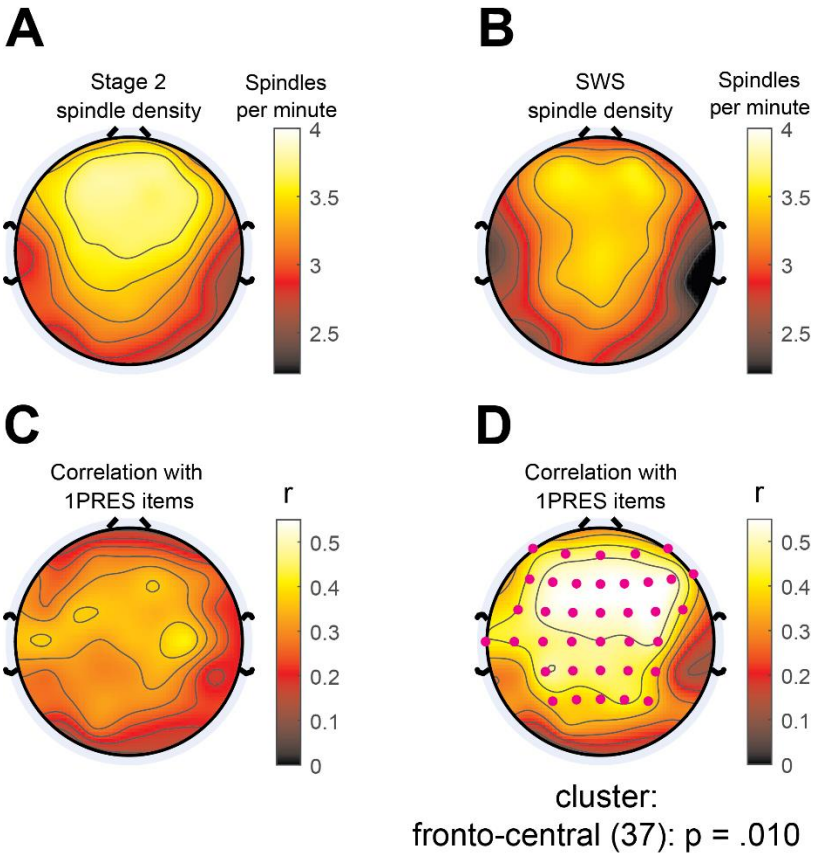

Figure 4. stage 2 and SWS spindles. **A** - Spindle density (spindles/min) in stage 2 sleep. **B** - Spindle density (spindles/min) in SWS sleep. **C** - Correlations between stage 2 spindle density change and recall for 1 PRES items. **D** - Correlations between SWS spindle density and change in recall for 1 PRES items. Electrodes with significant correlations following cluster correction indicated with pink dots.

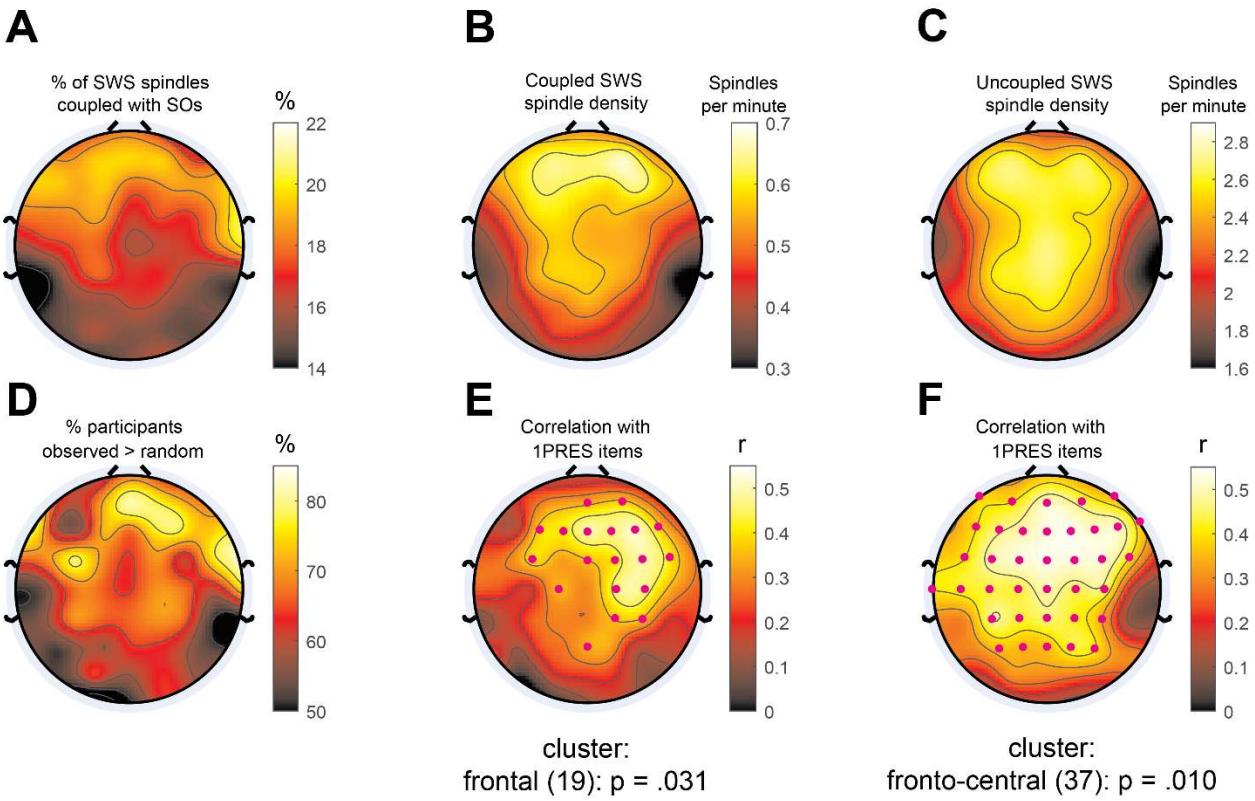

Figure 5. SWS slow oscillation-spindle coupling. **A** - Percentage of detected spindles coupled with slow oscillations. **B** - Coupled spindle density (spindles/min). **C** - Uncoupled spindle density (spindles/min). Note the difference in scale when comparing with coupled spindle density. **D** - Percentage of participant's whose degree of SO-spindle coupling is significantly greater than what would be expected by chance. **E** - Correlation between coupled spindle density and relative change in recall of 1 PRES items. **F** - Correlation between uncoupled spindle density and relative change in recall of 1 PRES items. SO = slow oscillation. Electrodes with significant correlations following FDR correction indicated with blue dots. Electrodes with significant correlations following cluster correction indicated with pink dots.

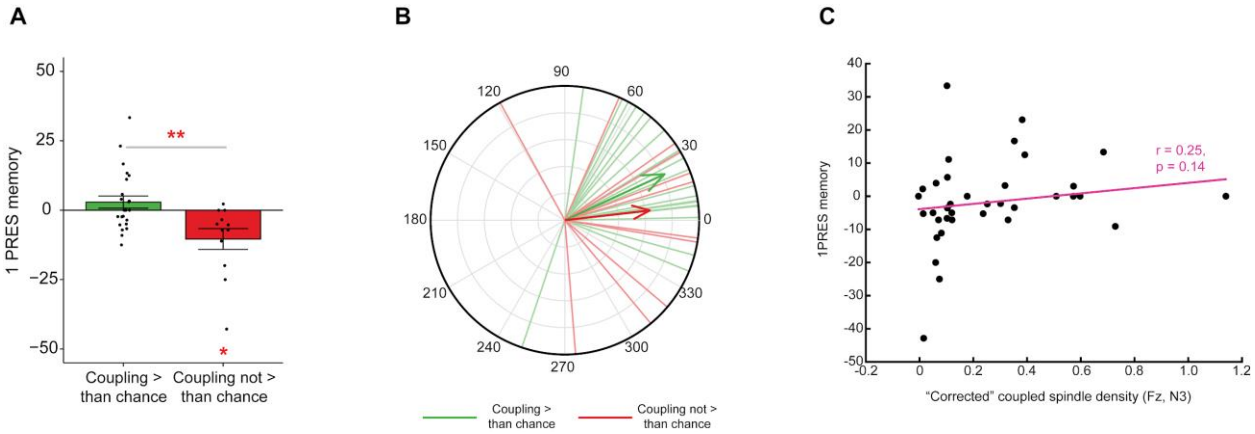

Figure 6. Coupling greater than and not greater than chance. **A** - Change in recall for 1 PRES items in participants whose slow oscillation-spindle coupling exceeded chance levels and participants whose coupling did not exceed chance. **B** - Coupling phase angle at Fz for those either exceeding or not exceeding chance level coupling. Mean phases within subject and group are depicted by lines and arrows respectively. The length of each arrow represents the within group coupling consistency. 0 degrees represents the positive peak of the slow oscillation. **C** - Correlation between "corrected" (observed - expected) coupling and change in recall for 1 PRES items. 1 PRES = 1 presentation, error bars show the standard error. ** = $p < .01$, * = $p < .05$. All coupling analyses from electrode Fz during SWS.