Slow Oscillations Modulate Overnight Brain Changes in Working Memory Function

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Abstract

Working memory (WM), the transient storage and manipulation of information, is a cognitive function that can improve with training. Accumulating evidence suggests that sleep, particularly slow oscillations (SOs) that occur during non-REM sleep, supports this improvement. Yet, how sleep, and SOs in particular, relate to neural processes supporting WM remain poorly understood. In this study, we investigated how WM-related neural activity evolves across nocturnal sleep and how these changes relate to neural processing during SOs. Participants performed a WM task during fMRI before and after sleep, with simultaneous EEG-fMRI capturing neural activity during the first 2.5 hours of sleep. Our results showed significant overnight changes in WM-related activity, characterized by reduced recruitment of the dorsal precuneus during WM encoding/maintenance phases and frontal regions during the retrieval phase of WM. Additionally, sleep increased item-specific reinstatement in a sensory processing region during WM. This pattern of results suggests a combined influence of sleep on enhancing sensory reinstatement while reducing potential top-down control (i.e., reduced parietal and frontal activity). Critically, SO-related activity was directly linked to overnight activity changes: stronger SO activation in the premotor cortex and ventromedial prefrontal cortex predicted greater overnight reductions in WM-related activity, and multivoxel analyses in the ventral attention network revealed a parallel relationship. These findings suggest that SOs play a critical role in WM function by facilitating the reorganization of WM-related processing.

Introduction

Working memory (WM) is a critical aspect of cognition that facilitates the temporary storage and manipulation of information to achieve goal-directed behavior. Beyond temporarily helping you remember a phone number until you can write it down, WM also supports a wide range of cognitive functions that are fundamental to many everyday tasks, such as decision-making, problem-solving, medication adherence, and language comprehension (Baddeley, 1992; Conway et al., 2002; Engle et al., 1999; Insel et al., 2006). Given its functional importance and its vulnerability to age-related decline (Hale et al., 2011), cognitive training to improve WM function has become a focus of research. The hope is that by improving WM, executive functions will also improve, which could mitigate cognitive aging. Several studies have demonstrated that a period of sleep, compared to wake, between WM sessions supports WM improvement (Zinke et al., 2018; Kuriyama et al., 2008; Lau et al., 2015; Chen, Whitehurst, & Mednick, 2020), with minutes in slow wave sleep (Dang-Vu et al., 2010; Takashima et al., 2006; Tononi & Cirelli, 2006) and power in low frequencies (slow wave activity (SWA, 0-4Hz)) (Cirelli, 2017; Maquet et al., 1997) and slow oscillations (SOs, 0-1Hz)) specifically implicated. After three weeks of WM training, increases in central-parietal SWA correlated with WM performance improvement(Pugin et al., 2015). Furthermore, SWA during post-training sleep predicted WM gains across a period of sleep in both young (Ferrarelli et al., 2019) and older adults (Sattari et al., 2019). Importantly, SWA may play a potentially causal role in WM improvement, as participants with greater SWA induced by an acoustic slow-wave stimulation during nighttime sleep showed better WM improvement, compared to individuals who did not show enhanced SWA (Diep et al., 2020). Additionally, the number of SOs that increase with changes in heart rate positively correlate with WM improvement overnight (Chen et al., 2021). Taken together, these studies support the role of sleep, specifically, low frequency activity in SWS, in WM improvement. And yet, how WM mechanisms shift across the night and their relation to SWS oscillations is not understood. The current study aims to bridge this gap by measuring neural processing during WM in the evening and morning, combined with simultaneous EEG-fMRI during intervening sleep.

WM engages a distributed network of brain regions, including portions of the prefrontal cortex, parietal cortex, and the precuneus (Chai et al., 2018; Christophel et al., 2017; Cohen et al., 1994; D'Esposito et al., 2000; Diwadkar et al., 2000; Levy & Goldman-Rakic, 2000; Nee et al., 2013). Two major attention networks contribute to WM: the dorsal attention network - comprised of the intraparietal sulcus (IPS) and the superior frontal gyrus (SFG) - and the ventral attention (or salience) network, including the temporoparietal junction (TPJ), inferior frontal cortex, the anterior insula, and the dorsal anterior cingulate cortex (Corbetta et al., 2008; Majerus et al., 2006, 2012). The dorsal attention network is associated with top-down task-focused attention and WM load (Majerus et al., 2018), whereas the ventral attention network is thought to govern bottom-up attention, particularly in response to novel or salient stimuli, as well as facilitating switching between internal and external attention (Asplund et al., 2010; Cabeza et al., 2012; Schimmelpfennig et al., 2023; Zhao et al., 2022). Training induced changes in WM capacity reflect plasticity in WM-related brain activity patterns (Au et al., 2015; Jaeggi et al., 2008; Karbach & Verhaeghen, 2014), including increased activation in the prefrontal (Miller et al., 2022) and parietal regions (Olesen et al., 2004), and decreased functional connectivity within the striatal-prefrontal network (Lin et al., 2017). WM relies on multiple component processes, including encoding new information, maintaining them over short delays, and retrieving them when needed. Although encoding and maintenance have been more extensively studied, active retrieval of

representations is particularly important during situations requiring complex WM, such as when distractors interfere with WM maintenance (D'Esposito & Postle, 2015; Muhle-Karbe et al., 2021; Souza & Oberauer, 2016). Evidence from a meta-analysis suggests that these core WM processes may engage distinct neural networks (Kim, 2019). However, it remains unknown how sleep influences these dissociable aspects of WM and the large-scale networks that support them.

This study investigates neural mechanisms of sleep-related WM improvement by 1) investigating overnight changes in WM-related brain activity and 2) linking such overnight changes to neural processing during SO windows (Ilhan-Bayrakcı et al., 2022). We employed the operational span (OSPAN) task, a complex WM task which measures the ability to encode, maintain, and subsequently retrieve a set of sequential items in WM, while a secondary (distractor) math task is performed. Prior work has shown that the OSPAN task is sensitive to changes in WM function across sleep (Chen, Whitehurst, Naji, et al., 2020; Sattari et al., 2019), which motivated us to choose this task as opposed to other WM tasks (e.g. delayed match to sample (Daniel et al., 2016)). Participants performed the OSPAN task during fMRI in the evening, then slept while their brain activity was recorded using simultaneous EEG-fMRI (Figure 1a), and again performed the OSPAN task the following morning. Each participant completed two sessions separated by a two-week washout to increase the robustness of our data.

To assess overnight changes in WM-related brain activity, we first used a data-driven analysis to test whether WM-related brain regions showed changes in activation across the night (i.e., increases or decreases between evening and morning sessions). To probe distinct phases of WM, we separately queried overnight changes in WM phases of encoding/maintenance (processes which overlap in the OSPAN task) and retrieval. Beyond changes in regional BOLD activity, we tested whether the fidelity of neural representations held in WM may be enhanced by sleep. To do so, given the complex nature of the OSPAN task, which involves sequential encoding and maintenance of items in the face of distraction, we drew on the framework of item-specific reinstatement. Item-specific reinstatement refers to the reactivation of neural patterns representing encoded items during retrieval, such that the brain activity specific to each item is reinstated to support retrieval. High-fidelity reinstatement is a key mechanism supporting successful retrieval from long-term memory (Kuhl & Chun, 2014; Ritchey et al., 2013; Tompary et al., 2016) and WM (Rose et al., 2016; Sprague et al., 2016; Wolff et al., 2017). Item-specific reinstatement is often indexed via fMRI using encoding–retrieval similarity (ERS) (Kuhl & Chun, 2014; Ritchey et al., 2013; Tompary et al., 2016), which quantifies the overlap between neural patterns at encoding and retrieval specific to a particular item. Given evidence that sleep improves WM performance, we hypothesized that sleep would enhance the fidelity of representations encoded and retrieved in the OSPAN task, such that item-specific reinstatement during retrieval would increase after sleep. Lastly, beyond how WM processing changes online during WM task performance, we explicitly examined associations between overnight changes in WM function/activity and neural processing during sleep. We primarily focused on SOs during NREM sleep, given prior evidence linking SOs to WM improvement. To do so, we used two complementary approaches: a data-driven analysis that examined how changes in WM-related brain activity across the night were linked to levels of activation during SOs; and *a priori* network-driven analysis focusing on links between patterns of overnight changes in WM-related activation and activation during SOs, specifically within the Dorsal and Ventral Attention Networks (Majerus et al., 2018; Vossel et al., 2014). Given that SOs co-occur with sleep spindles during NREM sleep, which have been linked to memory consolidation (Jegou et al., 2019; Petzka et al., 2022), we additionally examined whether spindle activity was linked with overnight WM-related neural changes.

To our knowledge, this is the first study to examine how WM processing changes overnight, and how these overnight changes in online WM activity may be associated with SOs-related neural activity during NREM sleep. By addressing these questions, we provide new insight into the mechanisms through which sleep reshapes WM function.

Methods

Participants

The study complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and was approved by the University of California, Irvine, IRB committee (HS# 2020-5912). Sixty healthy females (18-40y) signed informed consents. Sixteen participants withdrew from the study before the first experimental visit. Four participants withdrew during the first experimental visit, resulting in 40 participants completing the first visit. Six participants were excluded after the first experimental visit due to an inability to sleep in the scanner. In total, 34 participants (M_{age} = 25.91 ± 5.29 years, all right-handed) completed the entire study protocol consisting of two overnight visits. Participants had no current or history of major psychological or medical conditions or sleep disorders, and additionally were not taking any medications (e.g., hypnotics) that would affect cognitive function or sleep. All participants included in the study reported consistent sleep habits in advance of the study, with sleep times before 1 am and wake times before 10 am. Participants completed the Morningness-Eveningness Questionnaire (Horne & Östberg, 1976) and Epworth Sleepiness Scale (ESS) as screening assessments, with an acceptable range between 6-21 for Morningness-Eveningness Questionnaire and <15 for ESS. This dataset is part of a larger study examining the effects of menstrual cycle–related hormonal variation on sleep and memory, and therefore included only female participants

Sample Size Justification

Our sample size was informed by prior sleep EEG-fMRI and WM studies. Previous work has demonstrated robust whole-brain and ROI-level effects of working memory with 25 participants (Faraco et al., 2011) and reliable sleep-related reactivation effects with nine EEG–fMRI participants (Bergmann et al., 2012). These studies provided minimum thresholds for our design. However, given the novelty of the paradigm, a directly comparable study on which to base a formal power calculation was not available; we are not aware of prior studies examining overnight changes in WM activation and linking such changes to neural processing during SOs. We therefore recruited conservatively above prior thresholds, initially recruiting 60 participants to achieve a completed sample of approximately 30-35 participants, ensuring adequate statistical power and robustness. Substantial attrition is expected in overnight EEG-fMRI protocols due to factors such as inability to sleep in the scanner and motion-related data exclusion. In our study, the need to sample across menstrual cycle phases in female participants imposed additional scheduling constraints and contributed to withdrawal rates.

Procedure

All participants completed an orientation session to give consent and practice the OSPAN task, which occurred on a day prior to the experimental visits. During the practice session, participants practiced the OSPAN task by viewing it on a computer monitor and responding as they would with the response keypads in the MRI scanner. After task practice, participants spent 15 minutes in a mock scanner to get familiarized with sleeping in the scanner. All 34 participants completed two overnight experimental visits using an identical protocol, separated by a two-week washout period. On each experimental visit, the participant arrived at 8 PM to undergo a T1-weighted structural scan. Participants then performed the OSPAN task, followed by a paired associate learning task (unrelated to the OSPAN task and beyond the scope of the current paper), while fMRI was performed. Participants were then removed from the MRI scanner to prepare for bedtime, after which the EEG cap was placed. At around 11 pm, participants were placed in the MRI scanner and had a 2.5h sleep opportunity with continuous EEG-fMRI recording (Table 1). Participants were provided with earplugs (~33 dB sound attenuation), comfortably bedded on a viscoelastic mattress, and covered with a light blanket. The lights were turned off and subjects were equipped with an alarm bell to alert the experimenter and terminate the scan at any time. After awakening, subjects spent the remaining night in the adjacent sleep laboratory, during which their sleep was monitored using OURA ring (Table 2). Participants were woken up around 7:30 AM the next morning and returned to the scanner around 8 AM to perform the OSPAN task. The study visit timeline is shown on Figure 1a.

Task and stimuli

The task was programmed using MATLAB UI Figure; stimuli were displayed using a LCD monitor (1920×1080 pixels with a 120Hz framerate). Responses and response times (RT) were recorded using MR compatible response keypads. Participants performed the OSPAN task in a similar fashion to Faraco et al. (2011) (Faraco et al., 2011). Each run consisted of fixed alternating blocks of Encoding/Maintenance (E), Math (M), Serial Recognition (R), and Baseline, each lasting 28s except for Serial Recognition (21s) (Figure 1b). In the Encoding/Maintenance block, letter items were sequentially presented for 1 s each and participants were instructed to remember them in serial order (seven letters per block). In between letters, participants performed a distractor task and judged whether math equations were correct (each equation was shown for 3 s). Thus, Encoding/Maintenance blocks required item encoding and maintenance in the phase of distraction. Each Encoding/Maintenance block was followed by a Serial Recognition (R) block, in which participants identified the letter shown in each serial position (1-7) by choosing between four letters across seven prompts (one prompt for each encoded item). During Math blocks, participants also viewed math equations and judged if each was correct, but an asterisk replaced the letters between equations, matching timing to the Encoding/Maintenance blocks. In other words, the Encoding/Maintenance and Math blocks only differed based on the need to encode and maintain serially presented letters. The Baseline block required participants to indicate if an arrow was pointing to left or right, with each arrow presented for 3s and separated by an asterisk for 1s. Each fMRI run included 17 blocks arranged as: Encoding/Maintenance + Serial Recognition + Baseline + Math + Baseline, repeated three times, and ending with Encoding/Maintenance + Serial Recognition. Participants performed two consecutive runs per session, with each run lasting approximately 8 minutes.

WM Task Behavioral Analysis

To assess changes in WM performance across sleep, accuracy and response time (RT) during the Serial Recognition blocks were measured. We calculated the proportion of accurate responses in each block as: number of correct letters recognized in the correct order divided by total number of letters (7); therefore, the maximum score was one. WM performance was evaluated by averaging accuracy across both runs in a visit for each participant. A repeated measures ANOVA with within-subjects factors of time of day (AM/PM) and visit (1 or 2) was conducted to assess whether overnight changes in accuracy were consistent across visits. A follow-up paired t-test was conducted between AM and PM sessions to assess sleep-related changes in WM performance (Figure 1c). To further probe changes in WM across sleep, we calculated RT during the Serial Recognition blocks for the correct trials. RT was measured as the timing between the stimulus presentation time to response. Similar to accuracy, a repeated measures ANOVA was conducted on RT, using within-subjects factors of time of day and visit. Averaged RT was compared paired t-test between AM and PM sessions using a paired t-test.

MRI Acquisition

Participants were scanned at the Facility for Imaging and Brain Research at the University of California, Irvine on a 3 T Siemens Prisma MRI scanner (Siemens Medical Solutions), with a 32-channel head coil. High-resolution T1-weighted anatomical images were obtained using a standard MPRAGE sequence (TR = 2300 ms, TE = 2 ms, flip angle = 8°, sagittal slices, 0.8 × 0.8 × 0.8 mm voxel size, field of view = 256 × 256 mm). Blood Oxygen Level Dependent (BOLD) functional scans (T2*-weighted) were acquired using an echo planar imaging (EPI) sequence (TR = 2240 ms, TE = 30 ms, flip angle = 90°, FOV = 216 × 216 mm, 40 transversal slices, slice thickness = 3 mm, dist factor = 10%, 3.4 × 3.4 × 3 mm voxel size, continuous bottom-up slice acquisition order). These parameters were chosen to ensure that residual gradient artefacts (in the slice repetition rate of ~18 Hz) did not compromise the sleep spindle frequency range (12–16 Hz). Each run of sleep scan contains maximum of 4096 volumes (approx. 2.5hrs) restricted by scanner limit. Participants were free to terminate the scan at any time and they may choose to continue sleeping in the scanner if the scan ended prematurely (see suppl. Table 1 for # of TRs obtained for each participant). Each run of the OSPAN task consisted of 216 volumes and 4 dummy samples were discarded during the initial acquisition to account for equilibrium effects.

fMRI Preprocessing

For each of the BOLD runs, the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep 1.4.0. The BOLD reference was then co-registered to the T1w reference using flirt (FSL 5.0.9, Jenkinson and Smith 2001) with the boundary-based registration (Greve and Fischl 2009) cost-function. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson et al. 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox and Hyde 1997, RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a transform to correct for head-motion. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space,

or just preprocessed BOLD. The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. Framewise displacement (FD) was calculated for each functional run via implementation in Nipype (following the definitions by (Power et al., 2015)). Physiological regressors were extracted to allow for component-based noise correction anatomical CompCor (aCompCor, (Behzadi et al., 2007)). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off). aCompCor components are calculated within the intersection of a subcortical mask (obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions) and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). All resampling was performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices and co-registrations to anatomical and MNI space). Gridded (volumetric) resampling were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Many internal operations of fMRIPrep use Nilearn 0.5.2 ((Abraham et al., 2014), RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation (https://github.com/nipreps/fmriprep). All analyses were performed on normalized MNI space data after spatially smoothing using a 5 mm full-width at half-maximum Gaussian smoothing kernel (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/).

EEG Acquisition

EEG was acquired with an MR-compatible 15-channel EEG cap (BrainCap MR, Easy-Cap, Munich, Germany) according to the 10-20 system. Scalp electrodes included Fpz, F3, F4, C3, C4, O1, and O2, referenced to FCz with AFz as ground. Bilateral mastoid electrodes (M1, M2) were included for re-referencing. Additional channels recorded electrooculogram (EOG1, EOG2), electromyogram (EMG1, EMG2, EMG3), and electrocardiogram (ECG) for artifact detection and sleep staging. Slow oscillation and sleep scoring analyses used the scalp and mastoid channels described above. Skin resistance was kept below 5 kΩ (plus 5 kΩ safety resistors) using Abralyt HiCl electrode paste (Easycap) to ensure stable EEG recordings during the 2.5 hr sleep opportunity. Bipolar recordings of electrooculogram (outer canthi), electromyogram (chin), and electrocardiogram (on the backbone, ~ 25 cm below and above the heart) were acquired via MR-compatible Ag–AgCl cup electrodes with 10 kΩ safety resistors (EasyCap). FCz was used as the reference electrode and Cz was used as the ground electrode. The data were recorded using BrainAmp MR plus DC and bipolar BrainAmp ExG MR amplifiers and the BrainVision Recorder (BrainProducts, Munich, Germany) with a resolution of 0.5 μV/bit at 5 kHz and filtered between 0.016 and 250 Hz. To ensure precise timing between EEG and fMRI data, we used the SyncBox (Brain Products, Munich, Germany), which synchronizes the clock of the BrainAmp MR amplifier with the clock driving the MRI scanner's gradient switching system.

EEG Preprocessing

Online MRI gradient and ballistocardiographic artifact correction (BrainVision RecView V.1.2; BrainProducts) allowed online sleep monitoring. Removal of these artifacts for subsequent

analyses was performed offline by adaptive template subtraction (Allen et al., 1998, 2000) using windows of 100 volumes and 50 pulses, respectively (BrainVision Analyzer V. 2.0; BrainProducts). EEG data were re-referenced to contralateral mastoids (M1 and M2) and sleep stages were visually scored in 30-second epochs following American Academy of Sleep Medicine (AASM) criteria. To ensure that only stable, continuous NREM sleep was analyzed, epochs containing movements or arousals were scored as motion artifacts. The MR helium cooling pump remained active during EEG-fMRI recording (Rothlübbers et al., 2015; Warbrick, 2022). All cleaned EEG data were visually inspected on an epoch-by-epoch basis during sleep scoring, and no evidence of systematic non-physiological noise patterns consistent with the helium pump interference was identified. Signal quality within the frequency bands of interest was preserved following standard artifact correction procedures, compared to our experience with EEG recordings outside of fMRI environments. Any residual non-systematic noise caused by the helium pump would be expected to reduce sensitivity to physiologically meaningful signals rather than introduce systematic confounds.

Slow Oscillations (SO) Detection

Individual SO events were detected in the EEG data from 65 sessions. Three sessions were excluded due to insufficient NREM sleep (two sessions with no NREM sleep and one session with inadequate NREM duration of less than two minutes). The detected SO events in C4 were then used as predictors in event-related fMRI analyses to assess BOLD activation during SO events (similar to (Ilhan-Bayrakcı et al., 2022)). SO troughs were detected for each channel automatically in MATLAB using the algorithm introduced by (Dang-Vu et al., 2008) (also used in (Chen et al., 2021; Niknazar et al., 2022)). EEG data were first band pass filtered within the SO frequency range (0.7-1.4Hz) using a Hamming windowed FIR filter. The Hilbert transform was then applied to find phase and amplitude of the SO. Troughs (down-states) were detected when the phase difference > 6. The up-states before and after each trough were then detected within 1.5 seconds window before and after the troughs. SO events were defined as the pre-trough up-states of SOs (event onset) through the post-trough up-states of SOs (defined as event offset) (Massimini et al., 2004; Mölle & Born, 2011; Zhang et al., 2020) during stable 30s epochs of NREM sleep (see definition in EEG Processing above). We detected on average 6.84 ± 7.98 SOs per minute across all of NREM sleep. A table of SO count and density by subject is included in supplementary materials (Supplemental Table 3). While our primary analysis focused on all SO events, we sought to probe whether relationships between SO activity and overnight WM activation changes may be due to coupling between SOs and spindle events, which have been implicated long-term memory. To test this, in a subset of analyses, we defined uncoupled SOs as those in which a spindle event did not occur within a ±1s window around the SO trough (see below for spindle event definition).

Spindle Detection

To examine BOLD activity related to sleep spindle events, spindles were detected using a validated automated algorithm applied to NREM epochs (Simon et al., 2021; Wamsley et al., 2013; Warby et al., 2014; Zhang et al., 2020). For each electrode, an individual spindle peak frequency was first estimated from the power spectrum by identifying the dominant spectral peak within 9-20 Hz. Spindle events were then detected using a Morlet wavelet-based spectrogram centered on this individual peak frequency (± 1.5 Hz), yielding a subject- and channel-specific detection band

that accounts for inter-individual variability in spindle frequency. Candidate events from C4 were retained if they exceeded four times the mean baseline power during clean NREM epochs and lasted at least 0.25 seconds, and were further refined by verifying that the instantaneous frequency, estimated from zero-crossings of the filtered signal, fell within 9-16 Hz, confirming the oscillatory morphology of each event and excluding non-spindle artifacts.

fMRI Analysis

General Linear Models (GLMs) were used to assess fMRI activation related to WM and sleep physiology (SO and spindle) events. First-level analyses (model specification and estimation) were performed using SPM12. Here, we describe general nuisance regressors and methods used for all GLMs, while the specific regressors and events of interest are described in the sections below (to measure WM-related activity, SO-related, and spindle-related activity). All scans were corrected for low-frequency trends in the GLM (high-pass filter with cut-off period = 111.111 seconds). To account for BOLD signal changes linked with head motion, nuisance regressors were created using framewise displacement (FD, output from fMRIPrep). Specifically, nuisance regressors were created for each time point surrounding head motion events (one TR before through to two TRs after FD > 0.5mm)(Power et al., 2015). The following nuisance regressors were included as covariates in all GLMs: high motion volumes (defined above), six motion parameters (translation x y z; rotation x y z), the 1st temporal derivative of the six motion parameters, and the top eight aCompCor (combined WM and CSF) components (Behzadi et al., 2007) (output from fMRIPrep). Beyond accounting for motion-related variance in each GLM, runs with excessive motion were excluded from analysis (% of excluded volumes greater than two standard deviations from the mean across all runs, separately for OSPAN and sleep runs). Additionally, one participant was excluded due to excess motion in most runs, and three participants had one session removed (either pm or am) due to excess motion in the majority of runs.

WM-related BOLD Activation

For each participant, we analyzed neural activation during both Encoding/Maintenance and Serial Recognition blocks of the OSPAN. Regressors were created to model BOLD activation during Encoding/Maintenance, Serial Recognition, Math, and Baseline blocks (in addition to the nuisance regressors describe above, fMRI Analysis). All blocks had the same duration (28s, with the exception of the Serial Recognition block being 21s), and onset times were calculated in 28s or 21s increments as the blocks alternated in their presentation. To assess encoding/maintenance, we contrasted activation during Encoding/Maintenance blocks with Math blocks in each session, generating separate contrast maps (beta estimates), separately for each AM and PM session. The Encoding/Maintenance vs. Math contrast yielded regions associated with the encoding and maintenance of letters as well as additional cognitive control required performing the secondary math task. Additionally, we contrasted activation during Serial Recognition vs. Baseline to assess retrieval-related activity.

To assess WM-related activation regardless of the time of day or sleep (Figure 2a), beta maps for each contrast type (Encoding/Maintenance vs. Math as well as Serial Recognition vs. Baseline) were averaged across all four sessions (PM and AM sessions and two visits) within each

participant. These average beta maps were then submitted to group-level analyses (described below).

To investigate overnight changes in WM-related processing, we used several complementary approaches. First, we asked whether the pattern of overnight activation change (between AM and PM sessions) was reliable across the two visits. To do so, we calculated the correlation of the pattern of AM-PM changes for the Encoding/Maintenance (vs. Math) contrast across gray matter voxels between the two visits in each participant. Then, to test whether the similarity (i.e., reliability) of AM-PM changes across visits was robust at the group-level (i.e., consistently greater than zero), we conducted a one-sample t-test on the Fisher Z-transformed correlation (r) values across participants.

Second, we used a standard group-level analysis to localize brain regions showing reliable changes between AM and PM sessions in WM-related activation. To characterize pre- versus post-sleep WM-related activation (Figure 2b), we averaged the contrast beta maps for pre-sleep (PM) and post-sleep (AM) sessions across both visits for each participant. Sleep-dependent WM changes (AM vs. PM) were then calculated as the difference between the AM and PM activation maps. These AM–PM beta maps were subsequently submitted to group-level analyses, as detailed below.

The contrast beta maps of WM-related activation were submitted to group-level analyses using one sample t-tests. Family-wise error (FWE) correction was performed using Randomise (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/) with TFCE (threshold-free-cluster enhancement) and 50,000 permutations. We first identified WM-related areas during encoding/maintenance at the whole-brain level by contrasting Encoding/Maintenance with Math blocks, averaged across AM and PM sessions. This revealed areas consistently engaged during WM encoding/maintenance phases, independent of time of day, that survived FWE-correction (Figure 2a, positive clusters). To assess overnight changes in WM encoding/maintenance, we then tested for AM–PM differences in the Encoding/Maintenance > Math contrast, restricting analyses to the WM-related mask defined above. We extended our analyses using the Serial Recognition > Baseline contrast to isolate retrieval-related activity. Overnight changes in retrieval were then assessed by comparing AM vs. PM activation within this contrast across the whole brain (FWE-corrected). The cerebellum was excluded from all analyses.

Changes in Item-specific WM Representations across Sleep

In addition to investigating changes in WM processing at the whole-brain level (described above), we tested the hypothesis that item-specific representations held in WM may change across sleep. To do so, we examined multi-voxel patterns in a sensory region involved in letter processing. We defined a sensory region involved in letter processing in the OSPAN task by contrasting activation to letter presentations during Encoding/Maintenance blocks vs. asterisks during Math blocks. This contrast yielded an area in the left occipital cortex, spanning the lingual gyrus to the posterior portion of the fusiform gyrus (Region of Interest, ROI, defined at $t > 2.5$, Figure 3a). This ROI was chosen given its role in representing letter identity (McCandliss et al., 2003) and based on current theories of sensory recruitment during WM (C. S. Adam et al., 2022), making it an ideal target for assessing item-specific reinstatement of WM content.

To measure item-specific reinstatement during WM, we first estimated item-level activity patterns using a GLM. For each run of the OSPAN task, a GLM was fit to the Encoding/Maintenance and Serial Recognition blocks, such that each regressor in the GLM modeled each individual item (letter) presentation (1s during encoding, 3s during retrieval).

Additional regressors of no interest included math equations and nuisance regressors described above. Resulting beta estimates for each item served as item-specific activation patterns. Next, we applied a representational similarity analysis to quantify the correspondence between encoding and retrieval patterns. Specifically, we computed the Pearson correlation between the spatial activity pattern elicited by each item at encoding and the corresponding pattern during retrieval, providing a measure of Encoding-Retrieval Similarity (ERS) (Figure 3b) (Ritchey et al., 2013; Trelle et al., 2019). Correlation values were Fisher z-transformed. To index item-specific reinstatement, we compared correlations between encoding and retrieval patterns for the same item (Match) versus different items (Non-match). The difference between these two values served as our measure of item-specific reinstatement. Prior work has shown that neural reinstatement supports successful memory retrieval, suggesting that the reactivation of encoding-related patterns facilitates access to stored information (Kuhl et al., 2012; Ritchey et al., 2013). Therefore, we hypothesized that if sleep strengthens WM function, it may do so by enhancing item-specific reinstatement-i.e., by promoting the reactivation of content-specific neural patterns during retrieval. We hypothesized reinstatement to be greater following overnight sleep, reflecting improved access to item-level WM representations in the morning.

Sleep BOLD Activation

An event-related design was used to model brain activity associated with SO events vs. periods of non-SO NREM (N2+N3 sleep). Within each run of sleep scans, scans were corrected for low-frequency trends ('spm_filter' function; high-pass filter with cut-off period = 111.111 seconds). Next, to limit our analysis to stable NREM (N2+N3 sleep), artifact-free (as defined from the 30s segments of EEG) epochs of NREM sleep with a duration > 100 TRs (224 seconds) were extracted from the BOLD fMRI data and concatenated together (after low-frequency trends and the mean BOLD signal was removed). GLMs were then estimated on the concatenated NREM data to quantify SO-related activation. SO event onsets were defined as the pre-trough up states of the SOs, and event offsets were defined as the post-trough up states of the SOs (see SO Detection). All nuisance regressors described above were included in the model. For participants contributing usable NREM data (n = 33 participants; 65 sessions), GLMs were fit separately for each session, yielding one SO-related contrast image per session. These session-level contrast images were then entered into a second-level analysis to estimate group-level effects (i.e., across 65 sessions). The primary contrast (SO events vs. implicit baseline of non-SO NREM sleep) identified brain regions showing differential activation during SOs relative to ongoing NREM activity (Figure 4). An analogous procedure was used to model activation related to spindle events. Separate GLMs were created using spindle event onsets and durations, following the same concatenation and GLM construction described for SO events. This yielded contrasts to estimate spindle activation relative to NREM sleep.

Correlations between Overnight OSPAN Changes and SO Activity

To assess whether changes in overnight WM activity may be related to neural processing during SOs, we examined correlations between these events using two distinct approaches. First, we asked whether across-session variance in regional overnight changes in WM BOLD activity was related to variance in SO activation (Figure 5). To do so, we correlated the degree of overnight

WM activation changes (AM - PM Encoding/Maintenance vs. Math activation) with levels of SO activation across sessions at the voxel-wise level, using robust linear regression (the robustfit function in MATLAB) (Holland & Welsch, 1977), which automatically downweighs sessions with high variance (relative to the population, i.e., outliers). In other words, this analysis tested whether sessions with greater overnight changes in WM-related activation in a given brain region were associated with greater activation during SO events in sleep. Multiple comparisons were corrected using the Benjamini and Hochberg method with a false discovery rate $q < 0.05$ (significant clusters with an extent of > 5 voxels were reported). The scatterplot in Figure 5 illustrates the relationship between SO activation and overnight Encoding/Maintenance (vs. Math) activation change across each night averaged across all significant clusters.

In addition to the data-driven approach described above, we also used a network-driven approach to examine relationships between overnight changes in WM activity and SO activity. The goal of this analysis was to examine whether patterns of overnight WM activation changes across voxels were related to patterns of activation during SOs in those voxels. To do so, we focused on pre-defined networks implicated in attention. Specifically, we examined the Ventral Attention Network and Dorsal Attention Network, defined using the 7-network parcellation of the human cerebral cortex from Yeo et al. (2011) (Thomas Yeo et al., 2011). The Ventral Attention Network is shown on Figure 6a. To examine this relationship, we extracted the AM – PM change in activation (contrast value) and SO vs NREM activation (contrast value) and averaged these values across participants. We then performed robust linear regression to assess the correlation between overnight WM activity changes and SO activation across voxels (Figure 6c). The statistical significance of the observed correlation was assessed using a non-parametric permutation test. Specifically, we created a null distribution of correlation values by repeatedly shuffling the labels between the AM and PM sessions and re-computing the correlation between overnight WM changes and SO activation ($N = 1000$ permutations). Statistical significance (p-value shown in Figure 6c) was computed by comparing the observed correlation value to the null distribution.

To test whether the relationships described may be specific to SO activity, both analyses were additionally performed using sleep spindle events and uncoupled SOs (defined as SOs not temporally coupled with a spindle) in place of SO events. These analyses allowed us to examine whether links between overnight WM-related neural changes and sleep oscillatory activity are specific to SOs, or whether they extend to co-occurring spindle activity or SO-spindle coupling.

To further assess whether the association between SO activity and overnight activation change was specific to WM-related processes, we also conducted a linear mixed-effects (LME) analysis. In this model, voxel-wise SO activation was the dependent variable, and both WM-related overnight activation change (Encoding/Maintenance AM-PM) and the non-WM control contrast (Math AM-PM) were fixed-effects predictors, with subject included as a random intercept. This analysis allowed us to test whether the association between SO activity and overnight WM-related change remained significant after accounting for variance explained by the Math contrast, thereby quantifying the specificity of the SO-WM association.

Results

Sleep Architecture

On average, participants had 95.67 min (SD=36.62) of total sleep time in the MRI scanner (Table 1). The average sleep latency was 11.34 min (SD=12.73). The average duration of N2 sleep was 46.15 min (SD=22.59) and 36.3 min (SD=26.24) for N3. NREM sleep from 34 participants (66 nights) was included in the analyses as two sessions were excluded due to the absence of NREM sleep during the in-scanner EEG-fMRI recording (for individual sleep architecture, see Supplemental Table 2). Throughout the night (sleep in the scanner + subsequent sleep outside of the scanner), participants were in bed for an average of 493.24 min (SD=73.78), with a total sleep time of 366.06 min (SD=108.39). OURA categorizes NREM sleep into Light and Deep sleep, which we combined with N2 and N3, respectively (Table 2).

Behavioral Results

To assess changes in WM performance across sleep, 2-way repeated measures ANOVAs (am/pm * visit 1/visit2) were performed. For WM accuracy, significant main effects of time of day ($F_{(1,33)}$=4.52, p=.04) and visit ($F_{(1,33)}$=10.94, p=.002) were found, but no interaction between the two $F_{(1,33)}$=1.92, p=.18). The main effect of time of day was driven by significantly better WM accuracy during the AM test (M=0.77±0.18) compared to the PM test (M=0.74±0.16) (t_{33}=-2.21, p=.03; Figure 1c), demonstrating an overnight improvement in WM. Since no difference in overnight WM accuracy change was found across visits (no visit by time-of-day interaction), subsequent analyses measuring overnight changes in WM processing were performed on the data averaged across the two visits (Figure S1).

For RT, a 2-way repeated measures ANOVA (am/pm * visit 1/visit2) resulted in significant main effects of time of day ($F_{(1,33)}$=5.89, p=.02) and visit ($F_{(1,33)}$=8.52, p=.002), with a marginal interaction between the two $F_{(1,33)}$=4.31, p=.05; Figure S1). Participants had significantly faster responses in the AM (M=1.19±0.31 s) compared to PM (M=1.26±0.29 s) for all correct trials (t_{33}=2.43, p=.02). Together, these results demonstrate that WM function improved across sleep in our study, both in faster and more accurate responses, as expected from prior work (Chen, Whitehurst, Naji, et al., 2020; Kuriyama et al., 2008; Lau et al., 2015).

Neuroimaging Results

1) Overnight changes in working memory related activation

We first asked whether changes in WM function across different nights of sleep were reliable in our dataset. To do so, we measured the whole-brain voxel-wise pattern of overnight activation change (Encoding/Maintenance phases) for each visit and asked if this pattern of overnight change was reliable (i.e., correlated) between the two visits in each participant. The correlation in overnight WM-related activity change was significantly greater from zero (AM – PM; Mean r=0.06, t_{27}=2.34, p=.03, Figure S2). This indicates that patterns of WM-related activation change were not random across the brain but instead showed reliable regional changes across visits. The modest magnitude of this correlation is expected given that the analysis includes all brain voxels, the majority of which may not show meaningful WM-related overnight change, and is consistent with values reported in prior work using comparable voxel-wise pattern similarity

approaches (e.g. Tambini et al., 2017). This metric is therefore best interpreted as evidence that the overnight neural change pattern has a reliable spatial structure, rather than as an index of the strength of overnight WM-related plasticity per se. This motivated 1) our approach of combining the two visits' data for subsequent neural analyses and 2) examining or localizing where in the brain overnight WM-related changes were reliable across participants.

Before isolating specific brain regions that showed overnight changes in WM activation, we characterized general activation associated with WM in our dataset (WM-related regions). To do so, we examined the Encoding/Maintenance vs. Math contrast at the whole-brain level across all sessions. Greater activation during Encoding/Maintenance compared to Math blocks was present in several cortical and subcortical areas (Figure 2a warm color), including the bilateral precentral gyrus, primary motor cortex, dorsal anterior cingulate cortex, caudate, anterior insular cortex, thalamus, putamen, occipital cortex and dorsal precuneus. Conversely, activation was reduced during Encoding/Maintenance compared to Math blocks in dorsal medial prefrontal cortex (PFC), anterior frontal, inferior parietal areas, and left lateral temporal cortex (Figure 2a cold color, FWE-corrected at $p<.05$).

To assess whether WM-related activation differed between PM and AM sessions, we first characterized WM activation in PM and AM sessions separately. During the PM session, we found widespread activation during Encoding/Maintenance vs Math blocks encompassing the frontal and parietal cortices (Figure 2b blue, FWE-corrected, $p<.05$), including the lateral PFC, premotor cortex, dorsal precuneus, dorsal anterior cingulate cortex, anterior insular cortex, putamen, caudate, occipital cortex, and supramarginal gyrus. In contrast, the AM session showed less WM-related activation (Figure 2b, red; FWE-corrected, $p<.05$), with activity localized to fewer regions, including the premotor and motor cortices, inferior frontal gyrus, and subcortical regions such as the cingulate and left putamen. These findings qualitatively suggest that fewer brain regions were reliably recruited for WM tasks in the morning compared to the evening.

To quantify overnight changes in activation during WM encoding and maintenance, we compared Encoding/Maintenance vs. Math activation between the AM and PM sessions (within WM-relevant regions, highlighted in Figure 2a, warm colors). A significant decrease in overnight activation was observed in the dorsal precuneus (MNI: 8, -59, 53.4; Figure 2c; FWE-corrected, $p<.05$), reflecting reduced activation during the morning compared to the evening.

In addition to WM encoding and maintenance phases, we performed a parallel analysis to probe regional changes in overnight activation during WM retrieval. Significant overnight decreases in activation during WM retrieval were observed in the postcentral gyrus (MNI: -12, -41, 67), precentral gyrus (MNI: -19, -25, 63), and frontal pole (MNI: -15.5, 40, 37) (Figure 2d; FWE-corrected, $p<.05$).

To address the possibility that circadian variation in neurovascular coupling or the global BOLD signal (GS) could confound analysis of overnight activation changes, we compared the GS amplitude between PM and AM sessions. No significant session-level difference in GS amplitude between PM and AM sessions was observed ($t_{35} = 1.45$, $p=.16$), indicating no systematic circadian shift in overall amplitude or magnitude of fluctuations in the global BOLD signal. As noted in the Discussion, the specificity of overnight changes to particular experimental conditions within each session (e.g., WM encoding/maintenance vs. Math contrasts), and their correlation with individual SO activity, further suggests that overnight changes were not driven by non-specific changes in the GS or neurovascular coupling.

In summary, we used multiple approaches to query overnight changes in WM-related processing. First, at the single-subject level, we observed reliable patterns of multi-voxel overnight

BOLD activity changes during WM (during encoding and maintenance periods). Second, on the group-level, we observed widespread WM-related activation during the PM session, whereas qualitatively fewer brain regions were recruited during the AM session. Quantitatively, the dorsal precuneus showed a significant overnight decrease in activation during WM encoding and maintenance, while regions throughout frontal and parietal cortex demonstrated significant overnight decreases during WM retrieval. These findings suggest reliable changes in neural engagement during WM after sleep.

2) Item representational changes across sleep

Sensory-recruitment theories predict that WM retrieval relies on the reinstatement of content-specific sensory representations. We therefore asked whether sleep enhances such reinstatement. Using independently defined letter-responsive ROI located in the occipital cortex (see Methods), we quantified ERS for each item. ERS is expected to be higher when retrieval patterns matched the encoding pattern of the same item (Match) than when they matched other items (Non-match), providing a metric of item-specific reinstatement. We then tested whether this reinstatement effect increased after sleep. In the PM sessions, ERS did not reliably differ between Match and Non-match pairs (t_{27}=−1.26, p=.22), indicating no detectable item-specific reinstatement before sleep. After sleep during AM session, ERS showed a robust reinstatement effect: Match pairs exhibited significantly greater similarity than Non-match pairs (t_{27}=2.34, p=.03, Figure 3c). Crucially, Match vs. Non-match ERS increased from PM to AM sessions (t_{27}=1.97, p=.05), reflecting an increase in item-level reinstatement across sleep. These findings suggest that sleep facilitates a refinement of WM neural representations, specifically by strengthening the reinstatement of item-specific patterns during retrieval. By enhancing neural reinstatement, sleep might lead to more robust item-specific, detailed sensory representations in WM.

3) Working memory BOLD Activation during SO

After investigating changes in WM activation across sleep, we next explored the specific mechanisms during sleep that contribute to these changes. First, we analyzed overall activation patterns during SO windows, compared to periods of NREM sleep outside of SOs, and observed a widespread decrease in activation in the frontal and occipital cortices (Figure 4a, cold colors) alongside increased activation in temporal and subcortical regions, including the cingulate and thalamus (Figure 4a, warm colors). Next, we examined whether WM-related regions (highlighted in Figure 2a, warm colors) were activated during SO events. Portions of the dorsal mid-cingulate cortex and right thalamus showed increased activation during SOs (Figure 4b, warm colors; FWE-corrected, p<.05). Decreased activation relative to non-SO NREM periods was observed in the anterior insular cortex, putamen, dorsal precuneus, and occipital cortex (Figure 4b, cold colors; FWE-corrected, p<.05).

These findings indicate that WM-related regions are actively modulated during SOs, raising further questions about how task-related WM activity is reflected during these critical windows of sleep.

4) Correlation between working memory and SO BOLD activation across sessions

To establish links between overnight changes in WM function and neural processing during SOs, we asked whether overnight WM activation changes were related to the extent of SO activation across sessions. For example, do sessions with larger overnight declines in WM activation show larger activation during SOs? We found a negative correlation between overnight WM changes (AM – PM) and SO-related activation in the ventral medial prefrontal cortex (vmPFC) and premotor cortex (Figure 5, FWE-corrected at $p<.05$, cluster extent threshold > 5 voxels). In other words, increased SO activity in these regions predicted greater post-sleep decreases in WM activation (Encoding/Maintenance vs. Math), implicating SOs in the reorganization of WM-related activity across sleep. In contrast, no regions showed significant associations when we repeated this analysis using retrieval-related WM activity, suggesting that SO-related modulation may be specific to encoding/maintenance processes rather than retrieval.

5) Spatial correlation between working memory and SO BOLD activation in the Ventral Attention Network

To investigate the potential role of neural processing during SOs in modulating overnight changes in WM function, we also examined pre-defined networks implicated in attention, the dorsal attention and ventral attention (salience) networks (Figure 6a). As a validation step, we first tested WM-related engagement of these networks by comparing activation during Encoding/Maintenance vs. Math blocks. The ventral attention network showed greater activation during Encoding/Maintenance vs. Math blocks ($t_{27}=3.02$, $p=.005$), whereas the dorsal attention network did not ($t_{27}=1.62$, $p=.11$).

Next, to determine whether SO-related activity is associated with overnight changes in WM activity, we examined the relation between multi-voxel patterns of overnight (AM-PM) Encoding/Maintenance activation changes and SO activation. Across voxels in the ventral attention network, there was a negative correlation between patterns of overnight Encoding/Maintenance activation change and SO activation ($r=-0.27$, $p=.01$, Figure 6b, top). This indicates that voxels with greater overnight reductions in WM activation showed stronger activation during SO events. Importantly, this correlation was specific to WM-related activation, as overnight changes in Math activity (Math vs. Baseline) were not significantly correlated with SO activity ($r = -0.1$, $p=.54$). A direct comparison of the two correlations confirmed a significant difference ($p_{perm} = .046$), indicating that the association between SO activity and overnight activation change was stronger for WM encoding/maintenance than for the non-WM control (Math). Moreover, in a joint LME including both predictors, the association between overnight Encoding/Maintenance activation and SO activity remained significant after accounting for Math activation ($\beta = –14.94$, $p < .0001$), reinforcing the specificity of this effect to WM-related processes. Finally, this pattern of correlation was unique to the ventral attention network: no significant correlation between overnight Encoding/Maintenance changes and SO activity was observed in the dorsal attention network ($r=-0.11$, $p=.25$).

In summary, patterns of overnight changes in WM activity were correlated with SO activity in the ventral attention network, suggesting that SO activity may facilitate overnight reductions in WM activation. This finding was not observed for overnight activity changes associated with other aspects of cognition (e.g., Math) or the dorsal attention network, highlighting the specificity of the relation between SO activity and WM-related neural processes.

6) Specificity of the SO-WM correlation: complementary analyses with spindles and uncoupled SOs

There are other oscillatory events during NREM sleep like sleep spindles that co-occur with SOs, raising the question of whether SO-WM relationships reflect SO dynamics specifically or are driven by their temporal overlap with sleep spindles. To address this possibility, we repeated the correlation analyses (Figures 5 and 6) using spindle-related BOLD activation and uncoupled SO-related BOLD activation (SOs not co-occurring with a spindle) as predictors of overnight WM-related neural change. If relationships are driven by spindles and/or SO-spindle coupling, and not by SOs in isolation, we expect them to be similarly present during spindle events alone and reduced when analyzing uncoupled SOs (in isolation of spindles). However, if relationships are specific to SOs, they would be absent during spindle events and similarly present during uncoupled SOs.

Whole-brain analysis. Spindle activation showed no significant association with overnight WM-related changes in any voxel cluster at the whole-brain level. In contrast, uncoupled SO activation yielded a significant voxel-wise association with overnight WM-related changes in the vmPFC adjacent to, and closely paralleling the main SO findings (Figure S3). This pattern is consistent with the view that the regional frontal SO-WM relationship reflects SO dynamics in isolation, rather than their co-occurrence with spindles.

Multivariate pattern analysis within the ventral attention network. The results were less consistent across event types. As expected, spindle activation ($r = 0.12$, $p = .18$, Figure S4) did not show a significant cross-session correlation with overnight WM-related changes within the ventral attention network, ruling out the contribution of spindles alone. However, uncoupled SO activation similarly did not reach significance ($r = 0.17$, $p = .22$, Figure S4). This suggests that the multivariate pattern relationship observed for the full SO event set may depend, at least in part, on the inclusion of SOs coupled with spindles.

Discussion:

In this study, we used simultaneous EEG-fMRI to investigate the neural basis of WM improvement across sleep. To our knowledge, this is the first study to demonstrate how sleep physiology, specifically SOs, may orchestrate functional changes in the brain associated with overnight WM improvement. Our findings offer several insights into how neural mechanisms supporting WM change in relation to sleep. First, we observed reduced BOLD activation after sleep during WM encoding, maintenance, and retrieval, indicating a role for sleep in the streamlining of neural engagement with WM training. Second, sleep enhanced item-specific memory reinstatement during WM: neural patterns during retrieval showed a stronger resemblance or reactivation to those elicited by the same item at encoding, compared to different items. Finally, we identified a potential role for SOs during sleep in modulating overnight WM BOLD activation changes. Specifically, stronger activation in the vmPFC and premotor cortex during SOs was associated with greater overnight reductions in WM activation. Moreover, in the ventral attention network, multivoxel activation patterns during SOs were spatially correlated with patterns of overnight reductions in WM activity. Notably, this correlation was specific to WM encoding and maintenance and not observed for non-WM processing (Math). Together, these findings provide

evidence that SOs may play a critical role in modulating neural processes underlying WM improvement across the night.

WM does not operate in isolation but is deeply interconnected with broader learning and memory consolidation processes. Theories of WM propose that task-relevant information is maintained by reactivating sensory and perceptual regions involved in encoding stimuli, highlighting the importance of domain-specific regions in representing and manipulating relevant information (D'Esposito & Postle, 2015; Hallenbeck et al., 2021; Nee & D'Esposito, 2018). Research shows that a 3-month training led to improved WM performance with trained stimuli, and this performance improvement might be due to enhanced item-level representations in the lateral prefrontal cortex (Miller et al., 2022). For semantic stimuli such as letters, WM additionally involves the temporary activation of long-term memory representations, integrating prior knowledge to guide task performance (Lewis-Peacock & Postle, 2008). Our findings extend these frameworks by showing that sleep selectively enhances the fidelity of item-specific reinstatement in a letter-processing region in occipital cortex. Specifically, after a night of sleep, we observed greater item-specific reinstatement, such that activation patterns during retrieval more closely matched the same item seen during encoding (compared to non-matching items), a pattern not observed before sleep. This finding suggests that sleep improves the fidelity of WM representations, enabling more precise reactivation of task-relevant information. This observation aligns with prior studies showing posterior cortical regions, such as the fusiform word area, store stimulus-specific information, while the prefrontal cortex provides top-down modulation to guide task performance (D'Esposito & Postle, 2015; Ester et al., 2015).

The increased item-specific reinstatement, coupled with reduced activation in WM-related areas after sleep, including the dorsal precuneus during encoding/maintenance and frontal regions during retrieval, may reflect a reorganization in neural resources during WM. Following sleep, brain activity patterns for previously encountered items, such as letters, show greater evidence of reinstatement during retrieval, potentially facilitating recognition and reducing the cognitive resources required to maintain or store this information in WM. This is consistent with Vahdat et al. (Vahdat et al., 2017), who showed that NREM sleep downscales initial cortically-dominant memory traces while strengthening subcortically-dominant traces, with enhanced putamen connectivity predicting overnight performance gains. These findings suggest that NREM sleep refines and stabilizes task-relevant neural representations, which may explain the limited transfer of WM training to untrained tasks (Beatty et al., 2015; Corbin & Camos, 2011; Sprenger et al., 2013). Specifically, transfer is most likely to occur when tasks share overlapping principles or knowledge structures (Lustig et al., 2009). As task-relevant information becomes more robustly reinstated in domain-specific regions like letter-processing occipital cortex, it is possible that reliance on top-down control from the PFC and parietal cortex decreases. By improving the fidelity of neural representations and reducing the recruitment of ancillary regions, sleep may support more specialized sensory processing that facilitates WM.

Building on these insights into how sleep enhances WM processing, a key question arises: What are the specific neural mechanisms during sleep that drive these improvements? To this end, our findings suggest NREM SOs as a candidate process. During SOs, we found a broad decrease in WM-related activity, consistent with prior reports of widespread decreases in frontal and parietal areas (Dang-Vu et al., 2008; Picchioni et al., 2011; Tagliazucchi et al., 2013; Wang et al., 2025) as well as subcortical areas, including the precuneus during NREM sleep using fMRI (Kaufmann et al., 2006) and PET (Maquet et al., 1997). These decreases align with the long-standing view of SWS as a state of quiescence, during which brain oxygen metabolism, cerebral blood flow, and

glucose metabolism are decreased compared to wakefulness and REM sleep (Czisch et al., 2004; Sawaya & Ingvar, 1989; Townsend et al., 1973). However, SOs periods are not a total silence of communication. We observed increased activation in the cingulate cortex and right thalamus during SOs compared to non-SO NREM periods, suggesting SOs coordinate WM-related networks by selectively engaging certain regions while silencing others. In line with this, a recent study has also shown that SOs are associated with thalamic activation, potentially optimizing memory-related networks (Wang et al., 2025).

Importantly, when probing direct associations between brain activity during SOs and during WM processing, we found that when WM-related areas were more active during SOs, they showed less activity (i.e., potentially requiring fewer resources) after compared to before sleep. We observed this negative correlation between SOs-related activation and WM task-related activation using two methods. First, we found a negative correlation between the extent of SO activity across sessions and reductions in WM activity in the premotor cortex and vmPFC, both regions that were engaged in WM processing in our dataset. Moreover, multivoxel activation patterns during SOs were similar, or tended to mirror patterns of overnight changes in WM function in the ventral attention network, such that voxels with greater activity during SOs showed larger reductions in overnight WM activity. Interestingly, this correlation between SO-related activation and WM-related areas was specific to an encoding and maintenance period and not retrieval, raising intriguing questions about how or whether sleep selectively enhances specific WM processes. Future studies are needed to explore the mechanisms underlying this specificity. These results show explicit links between SOs and overnight changes in WM function during online processing. Given the established role of SOs in contributing to neural communication supporting long-term memory (Demanuele et al., 2017), our results suggest that SOs may also serve as a temporal framework for systems-level communication that benefits both WM and episodic memory processes.

NREM sleep is characterized by multiple interacting oscillatory events, including SOs, sleep spindles, and their temporal coupling. A substantial body of work has demonstrated that spindle activity, and particularly SO-spindle coupling, plays a central role in hippocampal-dependent memory consolidation by coordinating cortical reactivation processes (Jegou et al., 2019; Petzka et al., 2022). Thus, an important question is how our SO-related findings relate to this broader framework of sleep-dependent plasticity. One possibility is that different cognitive processes rely on partially distinct configurations of these sleep oscillations. The Slow Oscillation Switch Model proposes that SOs may support multiple, potentially competing functions during sleep. In a long-term memory state, SOs are tightly coupled with spindles and hippocampal ripples, forming a coordinated "triple phase-locking" mechanism that facilitates hippocampal-cortical communication (Staresina et al., 2023). In contrast, in a WM state, SOs that are not engaged in such coupling may preferentially support cortical restoration and network efficiency within prefrontal systems, processes that may benefit WM performance (Chen et al., 2022).

Our complementary analyses examining WM-related activation during spindle windows and uncoupled-SOs offer partial support for this framework, though the picture is mixed. On one hand, spindle activity showed no significant association with overnight WM-related neural changes at the whole-brain level, and the regional vmPFC SO-WM relationship was preserved when analyzing uncoupled SOs, suggesting that the vmPFC effect is not driven by SO-spindle coupling. On the other hand, the multivariate pattern in the ventral attention network was not replicated for uncoupled SOs, and we did not directly compare effect sizes between coupled and uncoupled SO conditions, which limit specificity. These results should not be interpreted as

indicating that spindle activity is uninvolved in sleep-dependent WM processing. Rather, they suggest that, in the context of WM-related neural reorganization, at least some of the relevant variance in the vmPFC is linked to SO dynamics that do not require spindle co-occurrence, while the full pattern of effects, particularly within the ventral attention network, may involve a more complex interplay between SO and spindle activity. This interpretation is broadly consistent with the framework that WM improvement may rely less on hippocampal–cortical replay mechanisms and more on SO-mediated cortical processes (Chen et al., 2022).

The specific neural mechanism underlying the role of SOs in modulating WM-networks remains to be explored. One the one hand, studies have shown that SOs in N3 promote synaptic downscaling, which involves the weakening of synaptic connections that have been strongly activated during wakefulness (Tononi & Cirelli, 2006). This downscaling process is thought to help maintain the stability and efficiency of neural networks, preventing them from becoming overloaded and potentially facilitating cognitive functioning, including WM, by freeing up capacity for the encoding of new information during the upcoming wake period (Raven et al., 2018). Another potential mechanism of how SOs modulate WM-networks is through glymphatic clearance. The glymphatic system is responsible for brain-wide delivery of nutrients and clearance of waste via influx of cerebrospinal fluid (CSF) alongside perivascular spaces and through the brain (Jessen et al., 2015). Specifically, SWS is associated with glymphatic clearance, as studies have reported that SOs are temporally coupled with and precede cerebrospinal glymphatic clearance (Fultz et al., 2019; Hablitz et al., 2019). Thus, an indirect benefit of clearing metabolic waste products and toxic substances that accumulate in the brain might be to maintain the optimal functioning of the brain, including the networks involved in WM. Further research that elucidates multi-level brain activity during SOs across animal and human studies is needed to better understand the mechanism underlying SOs' modulation of WM-networks.

Our study has several limitations. While employing all-female participants reduced biological heterogeneity and increased sensitivity to detect sleep-WM relationships, it limits the generalizability of our findings. Sex differences in sleep physiology, including sleep spindles, and their hormonal modulation, have been reported (Driver et al., 2008; Mong & Cusmano, 2016), and sex may also influence WM-related neural activity and plasticity (Shirzadi et al., 2024). Therefore, the present results should be interpreted as specific to a female sample. Future studies including male participants and mixed-sex cohorts will be important to determine whether the observed sleep-WM relationships generalize across sexes. Another shortcoming is the limited sleep duration and the amount of recorded sleep events during the scan made it impossible to differentiate between SOs in N2 and N3, despite evidence that SOs differ in their characteristics across stages (Cox et al., 2018). Although the group-average N2 and N3 durations suggest sufficient stage-specific sleep at the aggregate level, the number of SO events per stage varied substantially across participants and sessions: 7 sessions had fewer than 10 SO events in N3 (see Supplemental Table 3), precluding reliable stage-specific GLM estimation in these participants. Future studies with longer in-scanner sleep opportunities will be better positioned to formally dissociate SO function across NREM stages. It remains to be explored how SOs modulate WM-related areas throughout the night as we were only able to collect EEG-fMRI data for the first sleep cycle (Chokroverty, 1994; Wu et al., 2012).

Another limitation lies in the design of the WM task. While the block design was optimized to probe encoding and maintenance (Faraco et al., 2011), it does not allow for a clean dissociation of encoding, maintenance, and retrieval processes, since encoding and maintenance are combined and involve multiple items simultaneously. This makes it more challenging to understand how

sleep modulates specific neural mechanisms that support each phase of WM, for example, whether sleep may influence WM capacity or the precision of items held in WM (Bays et al., 2024). Behaviorally, the magnitude of overnight WM improvement was consistent across the two visits as shown by the lack of significant visit by time-of-day interaction, which supports averaging across visits for neural analyses. Nevertheless, we acknowledge that gradual task-related neural adaptation across visits cannot be fully excluded (as shown by the improved performance across visits), and future longitudinal designs with wake control intervals would be needed to more cleanly dissociate sleep-dependent and practice-dependent neural changes.

Moreover, although our study focuses on WM-related functional changes during sleep, prior studies have shown WM and episodic memory may compete for limited resources during sleep, particularly during SOs (Chen et al., 2022). Therefore, it will be interesting to investigate how neural processing during SOs may reflect this competition between WM and episodic memory. Although this study focused on NREM SOs given the EEG-fMRI recording window, we do not exclude the contribution of REM sleep to overnight WM improvement. REM sleep has been implicated in various forms of memory consolidation, particularly for emotional and procedural content, and may interact with NREM processes to optimize the consolidation of newly acquired information (Walker & Stickgold, 2006). The Refine and Rescue Hypothesis (Shuster et al., 2025) proposes that REM sleep actively refines memory representations by weakening irrelevant memory traces, thereby reducing neural activation associated with less efficient processing. This inhibitory function is particularly relevant to the pattern of overnight WM changes observed here, where reductions in task-related activation were observed after a night of sleep with improved performance. Under this framework, REM sleep may complement NREM SO-mediated processes by selectively pruning task-irrelevant representations, together contributing to the more selective neural recruitment observed following sleep. Future studies using full-night neuroimaging will be necessary to disentangle the specific and potentially complementary contributions of NREM and REM sleep to overnight WM-related neural reorganization.

One possibility is that overnight changes in neural activity reflect circadian-related neurovascular confounds. However, multiple converging lines of evidence argue against this possibility. Specifically, our analyses examining overnight changes in WM contrasted particular fMRI epochs compared to other epochs within the same fMRI session (e.g., PM or AM sessions), including WM encoding/maintenance blocks versus WM retrieval versus baseline epochs. Any overnight changes in BOLD activity driven by non-specific or global factors such as circadian changes would be expected to be equally present in all task conditions and therefore would not be evident in condition-specific contrast. Moreover, non-specific neurovascular confounds would be expected to be global or brain-wide in nature rather than resulting in changes in punctate or isolated to specific brain regions (as we observed). Similarly, we also would not expect overnight changes driven by non-specific circadian confounds to be specifically related to measures of neural activation during specific sleep neurophysiological events. Additionally, we found no significant difference in global BOLD signal amplitude between PM and AM sessions, and our nuisance regressors accounted for the majority of global signal variance, suggesting global signal differences were unlikely to contribute to the observed findings. However, we note that we cannot fully exclude a contribution of circadian variation in neurovascular physiology to our overnight BOLD contrast estimates. Future studies incorporating direct measures of neurovascular coupling will be important for definitively ruling out such confounds in overnight neuroimaging designs.

In conclusion, our findings demonstrate that overnight sleep contributes to WM by modulating neural processing associated with WM. By identifying multiple links between SO-

related neural activity and overnight changes in WM function, our study highlights the importance of SOs in shaping the neural mechanisms that support WM. These results lay the groundwork for refining theoretical models of sleep-dependent WM improvement and provide insights into the interplay between sleep physiology and cognition. Furthermore, our findings hold potential translational relevance, offering a basis for the development of sleep-based interventions aimed at improving WM performance.

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Tables and Figures

Minutes	Mean(SD)
TIB	139.71(42.08)
TST	95.67(36.62)
SOL	11.34(12.73)
N1	10.64(12.79)
N2	46.15(22.59)
SWS	36.30(26.24)
REM	1.87(6.97)
WASO	16.42(23.99)
SE(%)	69.98(21.93)

Table 1. Sleep Architecture During EEG-fMRI Recording. Means ± SD. TIB, time in bed; TST, total sleep time; SOL, sleep onset latency; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep/slow-wave sleep; REM, nonrapid eye movement sleep; WASO, wake after sleep onset; SE, sleep efficiency.

Minutes	Mean(SD)
TIB	493.24(73.78)
TST	366.06(108.39)
Light	197.28(58.12)
Deep	140.01(46.07)
REM	74.33(132.95)
WASO	49.46(32.01)

Table 2. Sleep Architecture Total (in scanner + out of the scanner, measured by OURA)

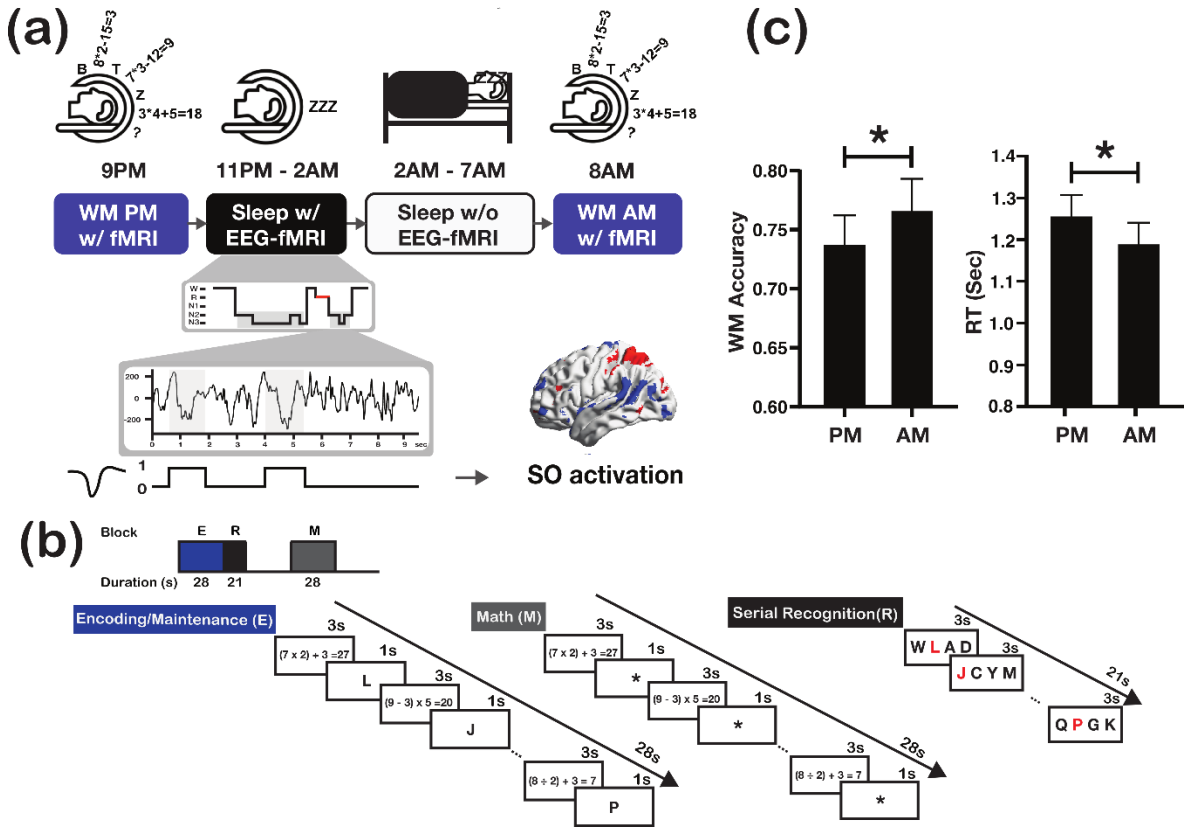
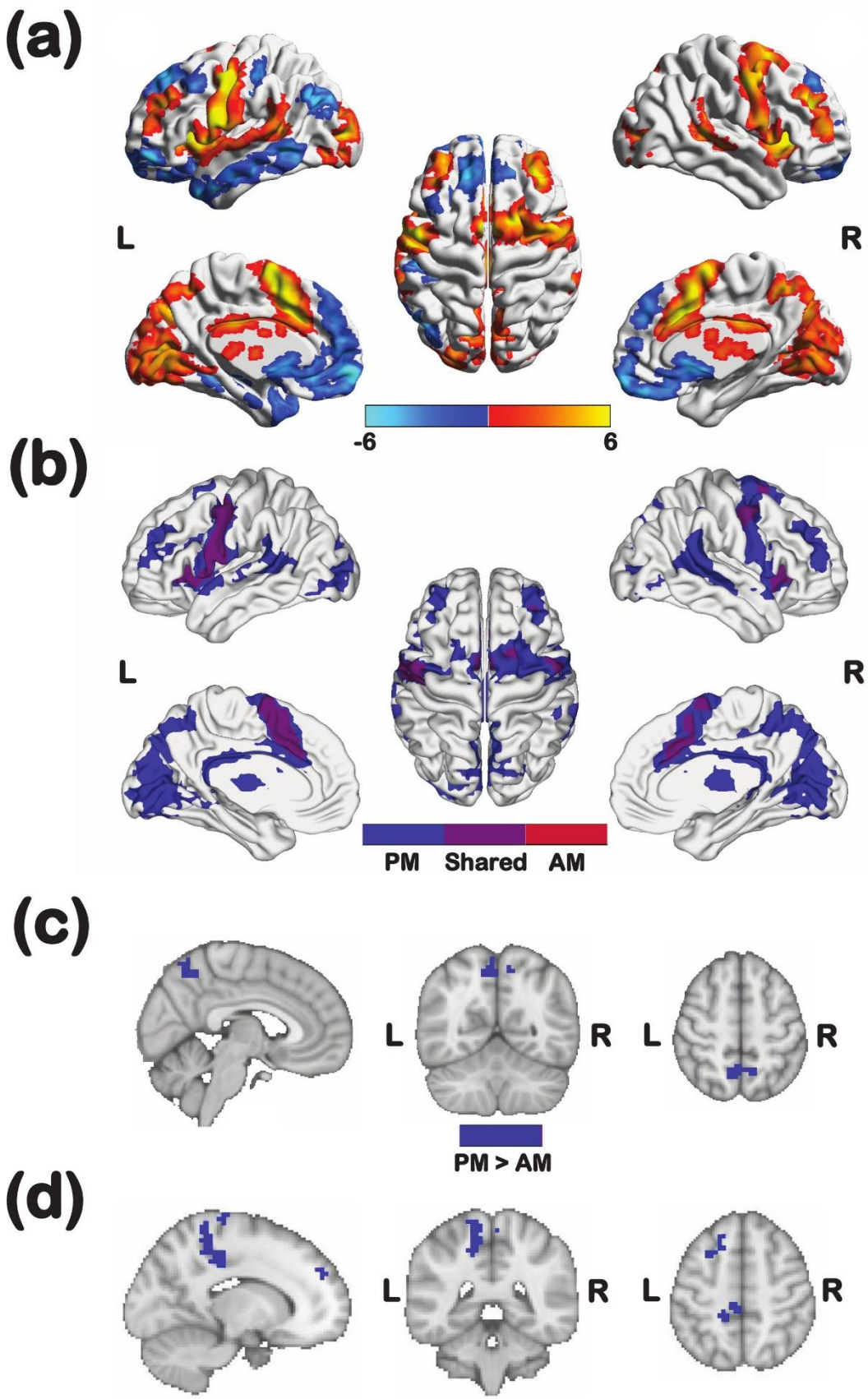


Figure 1. Study Timeline, Task Illustration and Performance. (a) Timeline of the study visit. (b) Illustration of WM task phases. (c) WM performance: **Left** – WM accuracy for PM (M = 0.74 ± SE 0.03) and AM (M = 0.77 ± SE 0.03) tests. **Right** – WM reaction time (RT) for PM (M = 1.26 ± SE 0.05 s) and AM (M = 1.19 ± SE 0.05 s) tests. Error bars indicate standard error (SE).


(a)
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(b)
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(c)
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(d)
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R
L
R

Figure 2. WM-related activations. (a) Whole-brain activation for the Encoding/Maintenance vs. Math contrast across all four sessions (t-statistic). Warm colors indicate regions with increased activation during Encoding/Maintenance vs Math, while cold colors indicate regions with decreased activation. (b) Regions showing significant WM-related activation (Encoding/Maintenance) in the PM session (blue), AM session (red), and shared across both sessions (purple) (FWE-corrected). Note that no AM-only (red) regions are visible in this figure because all regions showing significant WM-related activation in the AM session were also activated in the PM session (purple). (c) A cluster in the dorsal precuneus (MNI: 8, -59, 53.4) showing a significant decrease in activation overnight for the Encoding/Maintenance vs. Math contrast. (d) Clusters in the postcentral gyrus (MNI: -12, -41, 67), precentral gyrus (MNI: -19, -25, 63), and frontal pole (MNI: -15.5, 40, 37) showing a significant decrease in activation overnight for the Retrieval vs. Baseline contrast.

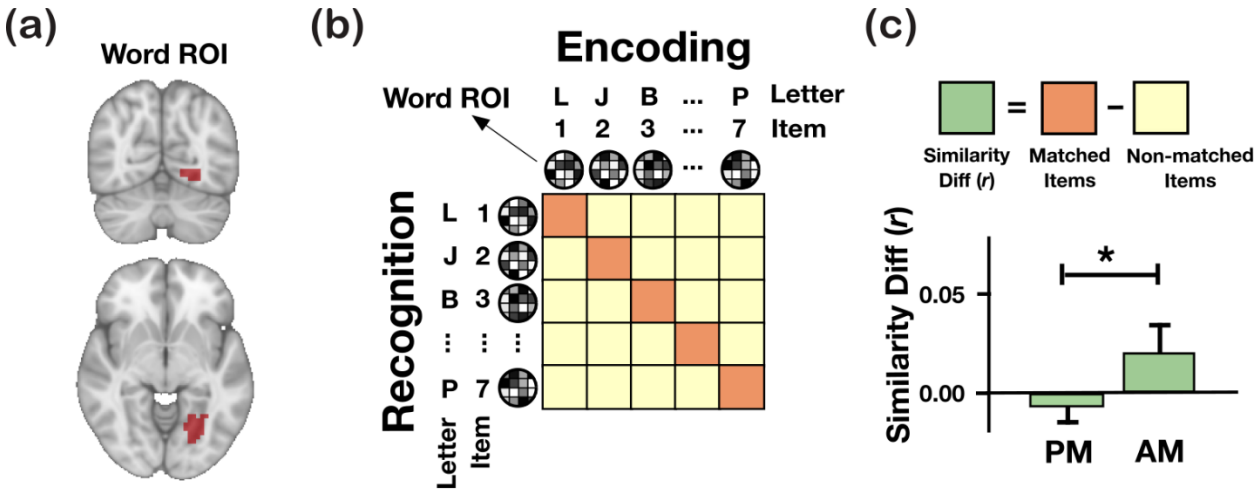

Figure 3. Item-Specific Reinstatement During PM and AM Testing. (a) Letter-responsive occipital ROI used for the reinstatement analysis. (b) Illustration of the item-wise multivoxel analysis approach. For each encoding–retrieval pair, we computed the correlation between multivoxel patterns to quantify similarity for the same item (Match – orange diagonal elements) and different items (Non-match – yellow off-diagonal elements), providing an index of item-specific reinstatement (Match – Non-match similarity). (c) The reinstatement Difference metric was significantly greater during AM than PM testing, consistent with enhanced item-specific reinstatement after sleep.

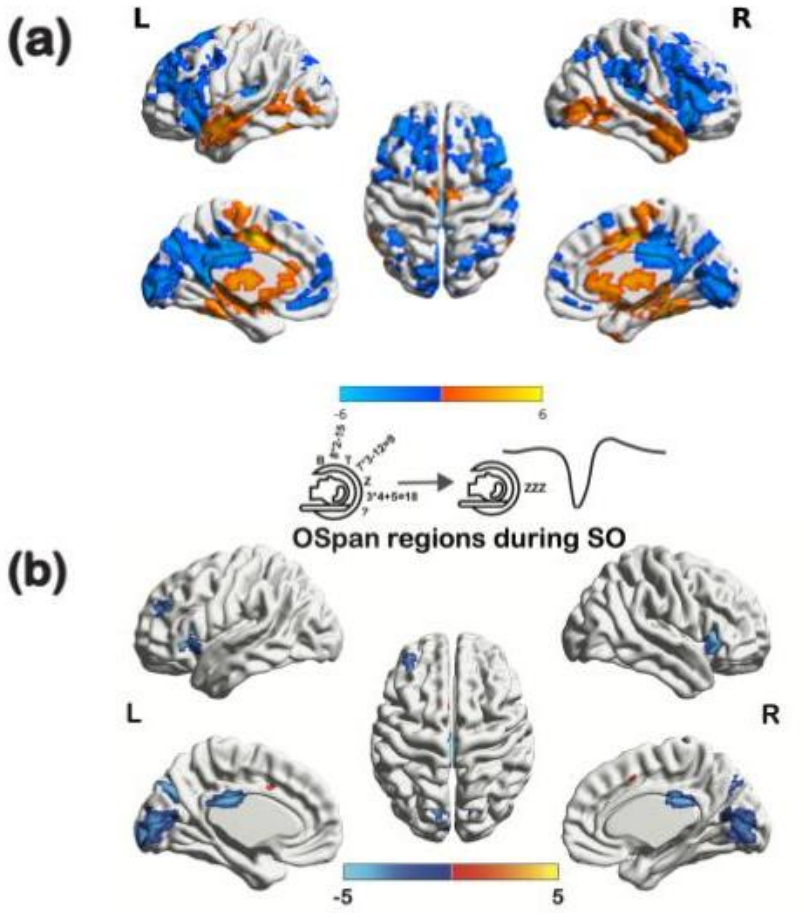

Figure 4. SO-related activations. (a) Whole-brain activation during SO windows compared to non-SO NREM periods. (b) Activation of WM regions during SO windows. Both maps show FWE-corrected t-statistics, with warm colors indicating higher activation during SO windows compared to non-SO NREM periods, while cold colors indicating reduced activation.

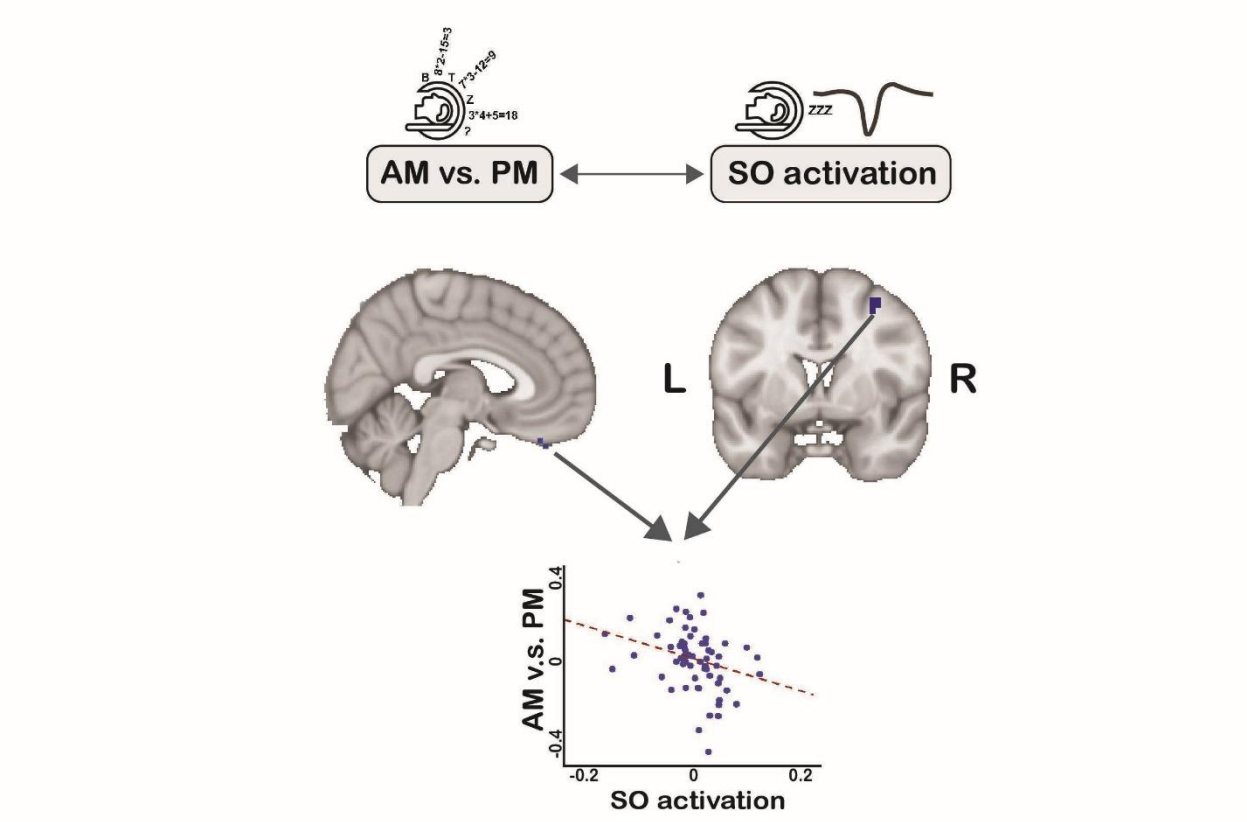

Figure 5. Correlation Between Overnight WM Activation Changes SO Activation. Significant clusters showing correlations between overnight changes in WM activation and SO activation, across sessions, were identified in the vmPFC and premotor cortex.

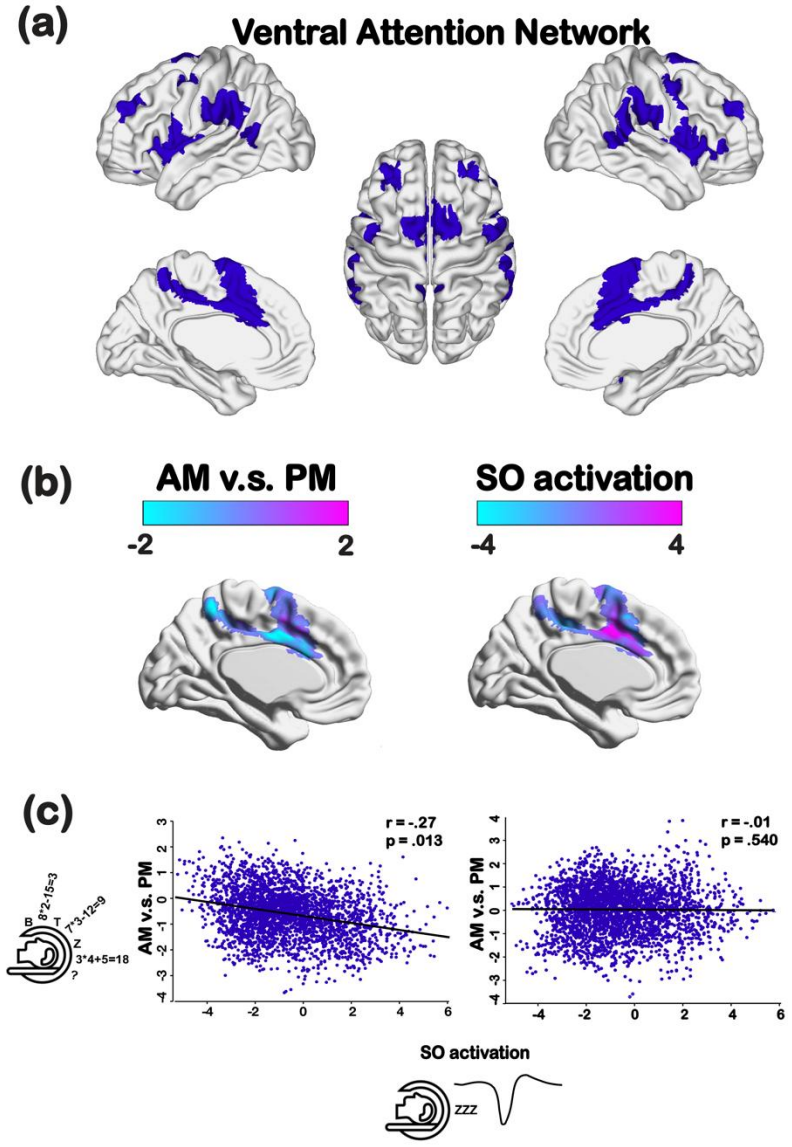

Figure 6. The Ventral Attention Network During WM task and SOs, and Their Correlation. (a) Representation of the ventral attention network (Yeo et al., 2011). (b) **Left**: Activation changes overnight (AM-PM) during Encoding/Maintenance vs. Math within the ventral attention network. **Right**: Activation of the ventral attention network during SO windows compared to non-SO NREM windows. (c) **Left**: Correlation between activation in the ventral attention network during SO windows and overnight (AM-PM) changes in Encoding/Maintenance vs Math. **Right**: Correlation between activation in the ventral attention network during SO windows and overnight (AM-PM) changes in Math vs Baseline.