ORIGINAL ARTICLE

Cued Memory Reactivation During SWS Abolishes the Beneficial Effect of Sleep on Abstraction

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Study Objectives: Extracting regularities from stimuli in our environment and generalizing these to new situations are fundamental processes in human cognition. Sleep has been shown to enhance these processes, possibly by facilitating reactivation-triggered memory reorganization. Here, we assessed whether cued reactivation during slow wave sleep (SWS) promotes the beneficial effect of sleep on abstraction of statistical regularities.

Methods: We used an auditory statistical learning task, in which the benefit of sleep has been firmly established. Participants were exposed to a probabilistically determined sequence of tones and subsequently tested for recognition of novel short sequences adhering to this same statistical pattern in both immediate and delayed recall sessions. In different groups, the exposure stream was replayed during SWS in the night between the recall sessions (SWS-replay group), in wake just before sleep (presleep replay group), or not at all (control group).

Results: Surprisingly, participants who received replay in sleep performed worse in the delayed recall session than the control and the presleep replay group. They also failed to show the association between SWS and task performance that has been observed in previous studies and was present in the controls. Importantly, sleep structure and sleep quality did not differ between groups, suggesting that replay during SWS did not impair sleep but rather disrupted or interfered with sleep-dependent mechanisms that underlie the extraction of the statistical pattern.

Conclusions: These findings raise important questions about the scope of cued memory reactivation and the mechanisms that underlie sleep-related generalization.

Keywords: sleep and memory, abstraction, memory reactivation, statistical learning

Statement of Significance

We demonstrate that experimental reactivation of memories during sleep can interfere with memory consolidation, leading to lower level of statistical knowledge the next day. Furthermore, such reactivation disrupts the otherwise systematic relationship between time spent in slow wave sleep and the degree of statistical abstraction. These findings are significant in that they provide an initial exploration of how memory replay in sleep interacts with abstraction processes, suggesting that mere reactivation may not always be the most useful way to process memories.

INTRODUCTION

Extracting statistical regularities from our environment, integrating them across different modalities, and generalizing to new exemplars or situations are fundamental processes in the formation of knowledge.[1,2] Accumulating evidence suggests that these processes of statistical learning and integrative processing are facilitated by sleep.[3–10] Specifically, sleep has been shown to promote the emergence of hidden rules or underlying patterns,[3–5,7,8] to transfer them across modality boundaries,[11] to strengthen connections between distinct elements,[6,9,12] and to facilitate the integration of new information with pre-existing knowledge.[13–15] The underlying mechanisms, however, are still unclear.

One hypothesis is that abstraction is facilitated by sleep through temporally overlapping reactivation of individual memories that share common elements, leading to a strengthening of the overlapping parts.[16] During sleep, memories are spontaneously reactivated,[17–21] leading to memory improvement.[22] Hippocampal reactivations are thought to be orchestrated at a neocortical level by slow neural oscillations during slow wave sleep (SWS).[23–26] According to this idea, the depolarizing up-phases of the slow oscillations drive the formation of spindle-ripple events. Spindle-ripple events grouped during slow oscillations may play a key role in hippocampal-neocortical dialog during sleep,[23,26–28] which may also underlie processes of abstraction and generalization.[16]

Spontaneously occurring reactivations during sleep can be manipulated by targeted memory reactivation (TMR).[29] During TMR, memory cues that are associated with a prior learning episode are represented during post-learning sleep and thought to bias or trigger spontaneously occurring reactivations, thereby manipulating the consolidation process.[29,30] In a series of recent studies, TMR has been successfully applied during SWS to increase the benefit of sleep on procedural and declarative memory.[31–36] Whether TMR can be used in a similar way to promote memory reorganization and processes of abstraction and generalization is largely unknown. The first evidence in support of this hypothesis was provided in a recent study by Batterink et al.[37] who showed that auditory cueing during sleep can influence grammatical rule learning and generalization. In this study, participants who were re-exposed to the language during sleep showed larger gains in grammatical generalization. These results are a first indication that memory reactivation during sleep may underlie abstraction and generalizing processes.

The current study aimed to further explore whether cued memory reactivation during SWS can be used to enhance the beneficial effect of sleep on abstraction of statistical regularities. We used an auditory statistical learning task, for which the benefit of sleep and the association between abstraction performance and SWS is well established.[7,8,11] In this task, participants are exposed to a sequence of tones that is probabilistically determined. Subsequently, participants are tested for recognition of short new sequences adhering to this same statistical structure. Performance in the recognition task therefore reflects whether the underlying statistical structure has been abstracted and can be applied to new exemplars. Additionally, a visual

version of the recall test exists, which allows to test whether regularities have generalized beyond the modality of learning.[11] Durrant et al.[16] showed that abstraction of the underlying statistical structure was enhanced after consolidation across sleep and predicted by the time spent in SWS. SWS also predicted a trade-off between recruitment of medial temporal lobe and striatum during subsequent use of this knowledge[8] and knowledge transfer to the visual modality.[11] In short, abstraction and generalization performance in this task clearly benefits from sleep, particularly SWS, and therefore presents a good target for cued memory reactivation.

To examine the effect of TMR during sleep in the present study, chunks of the probabilistic auditory sequence were represented during SWS in one group of participants. Another group, in which no TMR was applied, served as a control. To assess whether the effect of TMR was specific to sleep, the auditory sequence was represented during wakefulness directly before sleep in a third group of participants. Based on previous findings by Durrant et al.,[8,11,16] we expected to find general overnight performance improvement, further enhanced by TMR during SWS.

METHODS

Participants

Forty-two right-handed healthy volunteers participated in this experiment after informed consent was obtained, approved by the University of Manchester Research Ethics Committee. All had normal or corrected-to-normal vision, no hearing problems, and no history of neurological, psychiatric, or sleep disorders. Participants reported a regular sleep pattern over the month preceding the experiment and followed a standardized sleep schedule (11.00 pm–7.00 am) for 4 days prior to study begin. Participants were randomly assigned to one of three experimental groups (n = 14): SWS-replay (SWS-R) group (mean age: 22.86, standard deviation [SD]: 3.48, five females), control group (mean age: 22.50, SD: 3.44, six females) and presleep-replay (PS-R) group (mean age: 20.46, SD: 2.99, six females), which differed in terms of the replay.

Stimuli

The same stimuli were used in the current experiment as were used by Durrant et al.[7,8] The stimuli were made up of sequences of pure tones (lasting 200 ms each) with seven different frequencies (261.63, 288.86, 318.93, 352.12, 388.77, 429.24, and 473.92 Hz), which were obtained by dividing an octave into seven equal intervals in pitch space. These intervals are not heard in Western tonal music and were used in order to avoid creating melodic fragments familiar to Western listeners. Tones were sampled with a frequency of 44.1 Hz, had a fixed amplitude, and were Gaussian modulated to avoid aliasing edge effects. There was a 20-ms gap between tones in a sequence. The stimuli involved one exposure stream and 168 short test streams. The exposure stream consisted of 1818 tones and lasted 6 minutes and 40 seconds. The test streams consisted of 18 tones lasting 3.96 seconds each. In addition to the auditory test streams, the stimuli also involved 84 visual test streams, in which a yellow circle moved from left to right across a black background on the computer screen along 18 defined locations. On a computer screen with a resolution of 1024 × 768 pixels, the circle started in a location 62 pixels from the left edge of the screen where it remained for 200 ms. It then disappeared for 20 ms and appeared in its next location 53 pixels to the right, where it again remained for 200 ms. This process continued for 18 horizontal locations, giving the appearance of a circle moving across the screen in a series of discrete events. The vertical position for each event could take one of seven evenly spaced vertical locations (−250 pixels, −166.67 pixels, −83.333 pixels, 0 pixels, 83.333 pixels, 166.67 pixels, 250 pixels, relative to the center of the screen). The seven vertical locations were chosen in analogy with the seven possible pitch height locations in the auditory sequence. Auditory and visual sequences both consisted of discrete events over time, varying equally in height and following the same timings. Participants were not informed of this analogy.

The exposure stream, 42 of the auditory test streams and 42 of the visual test streams followed a probabilistic structure (structured condition). The probability for each potential transition between the current item (tone for the auditory stream and screen height for the visual stream) and the next item was determined by a transition matrix, forming a first-order Markov chain (Figure 1). In the transition matrix, each row contained one likely transition (p = .9, shown in white in Figure 1) and six unlikely transitions (p = .0167, shown in black in Figure 1). This ensured that a given item was followed by a particular item 90% of the time and by any of the other six items 10% of the time, making the sequences probabilistic. All seven items occurred overall with an equal probability (uniform zero-order transition), assuring that participants had to acquire sequence knowledge rather than just information on how frequently individual items occurred. The other half of the auditory and visual test streams (42 each) were generated randomly, with an equal probability for each tone/height at every position in the sequence (unstructured condition). As all test streams of the structured condition had the same probabilistic structure as the exposure stream, those test streams were considered as similar to the exposure stream, whereas the test streams of the unstructured condition were not similar to the exposure stream.

For the replay, the exposure stream was divided into six fragments, each 66-second long. All six fragments were played twice in randomized order, with a 10-second gap between the fragments. This replay stream had a length of approximately 15 minutes.

Experimental Task and Design

All three experimental groups followed the same basic protocol (shown in Figure 2), which involved two experimental sessions, one in the evening at 9.00 pm ± 1 hour and one the following morning at 8.00 am ± 1 hour. All participants slept the night (from 11 pm to 7.00 am) between the two sessions in a bedroom in the Sleep Research Laboratory at the University of Manchester, and their sleep was monitored using polysomnography (PSG). Before each session, alertness was measured using the Stanford Sleepiness Scale[38] (SSS) and the Karolinska Sleepiness Scale[39] (KSS).

Session 1 started with a learning phase lasting 8 minutes in which the auditory exposure stream was presented in order to familiarize participants with the transition probabilities. While

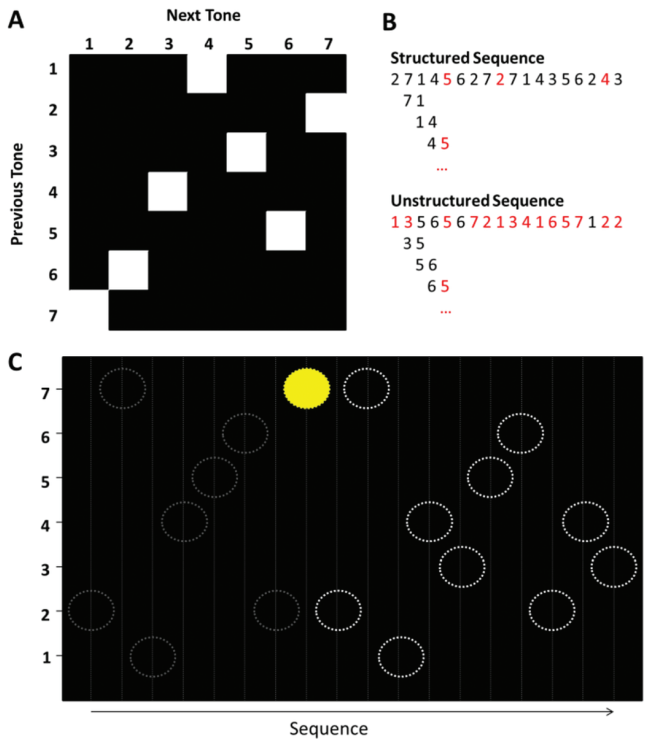

Figure 1—Generation of structured and unstructured sequences. (A) Transition matrix for the exposure stream and structured test sequences. Rows index the last tone that has occurred and columns tones that could occur next. The probability for each transition is reflected in the color with white = 0.9 and black = 0.0167. Tones occur overall with an equal frequency, ensuring that this cannot provide additional structural information. (B) Examples of a structured test stream and an unstructured test stream. Each test stream consisted of 18 tones. The sequence of structured test streams was determined based on the transition matrix, with the constraint that the number of high probability transitions was between 10 and 16. The sequence of unstructured test streams was generated randomly with an equal probability of 0.143 for each transition, resulting in four high probability transitions in this particular case. Low probability transitions are indicated in red. (C) Analogous to the auditory test streams, the visual test streams were sequences of a yellow circle moving from left to right across a black background. The circle started in the left edge of the screen and appeared at 18 distinct horizontal locations (indicated by vertical lines), giving the impression that it was moving from left to right. The vertical position could take one of seven evenly spaced locations, analogous to the seven pitch heights of the auditory streams. Structured and unstructured visual test streams were created analogous to auditory test streams.

the exposure stream was played, the term "Tone Stream" was presented in the middle of the computer screen, in order to focus participants' attention toward the auditory stream. Participants were informed that an immediate and a delayed recall task would follow, but they were not informed about the underlying probabilistic structure of the auditory stream.[8] Directly after the learning phase, participants conducted the immediate recall task which lasted 15 minutes. In this task, 42 structured and 42 unstructured auditory test streams were presented in randomized order. While a test stream was played, the instruction "Listen" as well as the number of the current trial out of the total number was presented in the middle of the computer screen ("Trial 18 of 84: Listen"). Subsequently, a 5-second response period (indicated by the phrase "Trial 18 of 84: Respond now") followed, in which participants indicated whether or not the test stream sounded similar to the exposure stream, by pressing correspondingly labeled buttons ("familiar" or "unfamiliar") on the computer keyboard. Participants were instructed to give their response as soon as they were sure. They were also informed in advance that half of the test streams were similar to the exposure stream and that the other half was unfamiliar.

The immediate recall task was followed by a two-back task (adapted from the study by Kane et al.[40]) which lasted 15 minutes. This task is a demanding working memory task, and it was presented here to provide an opportunity to replay the auditory stream to the PS-R group outside of the focus of attention. To avoid differences in the experimental design, which could potentially influence memory performance, the two-back task was conducted in all groups. In each trial of the two-back task, one of eight phonologically distinct letters (B, F, K, H, M, Q, R, X) was displayed in the middle of the screen for 500 ms, followed by a blank 2500 ms interstimulus interval. For each trial, starting from trial number three, participants attempted to press one button ("Yes") if the current letter matched the letter that appeared two items ago (B-f-b) and another button ("No") if the two letters did not match. Participants were instructed to respond as quickly and accurately as possible. Participants could give their response as soon as the letter appeared on the screen and until the end of the interstimulus interval. Following a short practice run, participants performed six blocks of 48 trials each. Within each block each letter appeared six times, once as a target and five times as a foil. To prevent recognition based on perceptual features only, letters appeared randomly in either upper or lower case. Participants were asked to maintain their focus on the task. After each block, feedback was given on accuracy and participants were encouraged to try to improve their performance in the following block. While participants completed this task, brown noise was played. Afterward electrodes were attached for the purpose of overnight monitoring and participants went to bed at 11.00 pm.

The following morning participants were woken up at 7.00 am. Session 2 started 30 minutes later with the delayed recall task. Trial structure and instructions of the delayed recall task were analogous to the immediate recall task, but 42 novel structured and 42 novel unstructured test streams were used. In the visual recall task, participants were presented with the 84 visual test sequences, in randomized order, and asked to indicate within the subsequent 5-second response period, whether or not the visual test streams were similar to the auditory exposure stream. Written instructions and the trial number out of the total number of trials were presented prior to each trial. In order to prevent participants from imagining the auditory analogue to the visual sequence, the seven different auditory tones were randomly played while the visual sequence was presented. Participants were instructed to ignore those tones and to use the visual information only in their judgment. Session 2 lasted 30 minutes (15 minutes for the auditory recall task and 15 minutes for the visual recall task).

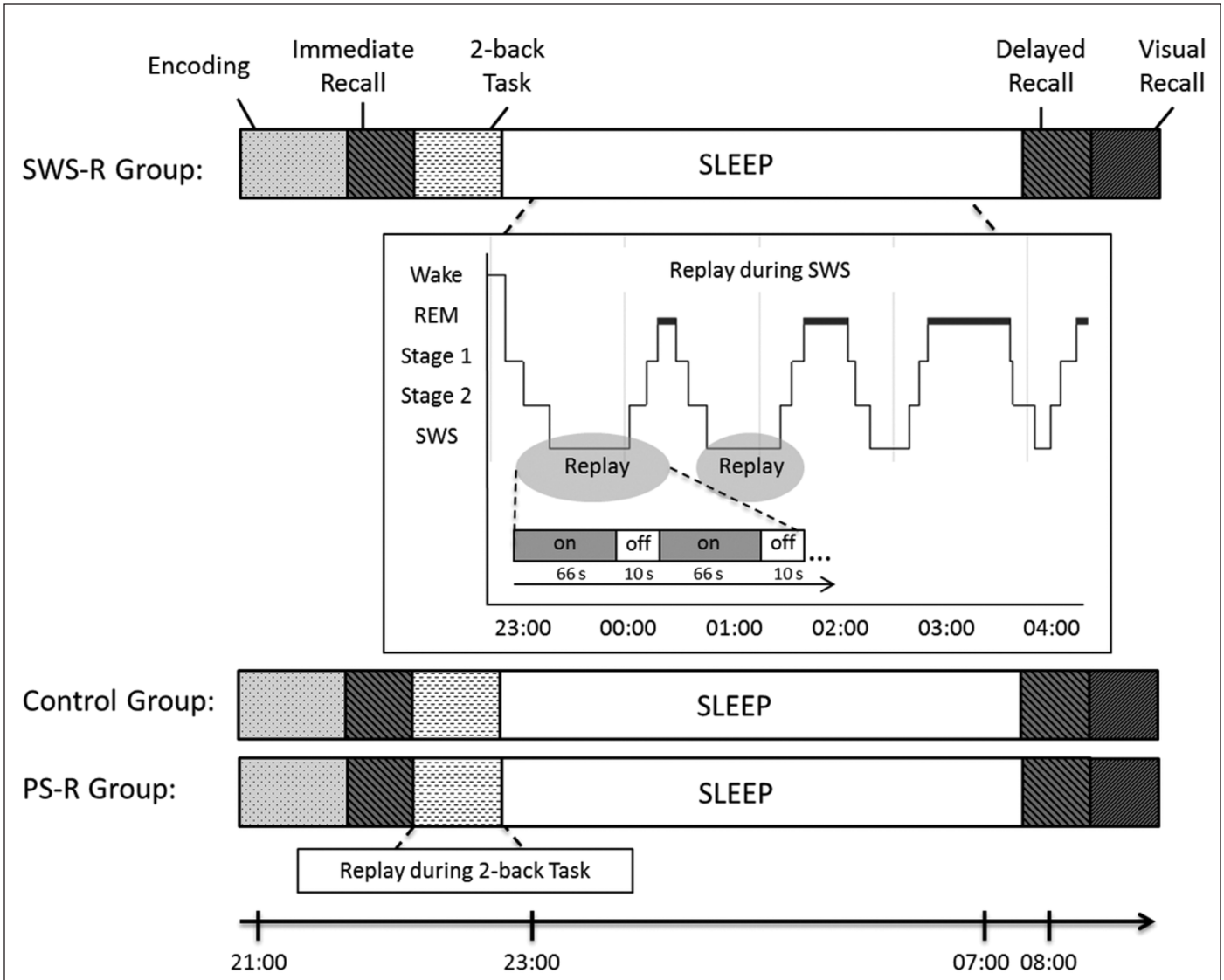

Figure 2—Experimental design. All groups encoded the exposure stream at 9.00 pm, followed by an immediate recall test session. Subsequently, participants completed a two-back working memory task. Overnight sleep was monitored with polysomnography. At 8.00 am, participants undertook a delayed recall session, followed by the visual recall task. In the SWS-replay (SWS-R) group the replay stream was presented during SWS and in the presleep-replay (PS-R) group during the two-back task. In the control group, no replay was done.

The three experimental groups differed in the presentation of the replay stream. In the SWS-R group, the replay stream was presented softly during the first two to three cycles of SWS. The replay started in the first extended period of SWS and was stopped immediately upon arousal or leaving SWS. In the PS-R group, the replay stream was presented during the two-back task. In both groups, the replay stream was played on PC speakers, with an approximate intensity of 48 dB, embedded in brown noise. In the control group no replay was done. In the PS-R group, the replay stream was presented during the two-back task, which served as distractor task and aimed to prevent rehearsal or active listening for a better comparison with the covert replay in the SWS-R group.

Equipment

The experimental tasks were realized using Cogent 2000 developed at the Functional Imaging Laboratory (University College, London), implemented using MATLAB© 7.5. Sound was generated using the onboard SoundMAX© digital audio chip and heard through a pair of Sennheiser © HD207 noise-cancelling headphones.

Behavioral Data Analysis

Data were analyzed with SPSS© 20.0 and MATLAB© 7.5. The sensitivity index d-prime (d' = z-score[hits]—z-score[-false alarms]) was calculated for the detection of the structured sequences for each session from the number of hits (correct identification of structured sequences) and the number of false alarms (incorrect identification of unstructured sequences as being structured). In cases where maximum hits or no false alarms occurred, half a trial was added or subtracted from the proportion correct when considering all test trials of the session (eg, 0.5/84) in order to avoid an infinite z-score.[41] The difference between the performance on the delayed and the

immediate recall session gave a measure of consolidation. A 2 × 3 mixed measures analysis of variance (ANOVA), with within-subject factor session (levels: immediate, delayed) and between-subject factor group (levels: SWS-R group, PS-R group, control group) was used on the d' measures to investigate performance differences between groups. A one-way ANOVA on the d' measures of the visual recall task was used to assess differences between groups. In all our results, we considered $p < .05$ as significant and all tests were two tailed. Significant effects were further explored with Bonferroni-corrected *t* tests. One-sample *t* tests were used to test if performance was above chance. For each round of the two-back task, the sensitivity index d-prime was calculated from the number of hits and false alarms. Differences between groups were assessed using a 3 × 6 mixed measures ANOVA with factors group and round (levels: round 1 to round 6).

PSG Data Acquisition and Analysis

An Embla© N7000 system was used for the EEG recording (200 Hz sampling rate). Six scalp electrodes were positioned using the international 10–20 system (F3, F4, C3, C4, O1, O2) with contralateral mastoid references. Two electrooculographic channels monitored eye movements and three chin electromyographic channels monitored muscle tone; a ground electrode was also attached. NuPrep© exfoliating agent was used to prepare the scalp, and electrodes were attached using EC2© electrogel. Impedance of less than 5 kΩ was verified at each electrode. Sleep data were visually scored using RemLogic© 1.1 software, in 30-second epochs, bandpass filtered between 0.3 and 35 Hz, by two trained sleep researchers according to the AASM Manual (American Academy of Sleep Medicine, Westchester, Illinois). Following the AASM recommendations, arousals were scored if there was an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles) that lasted at least 3 seconds, with at least 10 seconds of stable sleep preceding the change, incorporating information from occipital and central derivations.

The proportion of time spent in each sleep stage (stage 1, stage 2, SWS, REM) and the overall sleep duration were calculated. As previous studies showed that the amount of SWS predicted a performance increase from the immediate to the delayed recall session,[7,8] we measured the correlation between SWS and overnight performance change for all experimental groups. A multivariate ANOVA (MANOVA) on the time spent in each sleep stage was used to examine group differences in the sleep structure. For spindle detection, raw EEG data of nonrapid eye movement sleep (non-REM: including stage 2 and SWS) were cleaned of artifacts and bandpass filtered (12–15 Hz) using a linear finite impulse response filter in EEG lab v.9.0. An automated detection algorithm,[42] which counts amplitude fluctuations in the filtered time series, which exceed a predetermined threshold, as spindles, was used to determine the number of spindle events at each electrode. Reported results are averaged across frontal and central channels. Group differences were assessed using a one-way ANOVA. Power spectral density during SWS was analyzed on central (averaged across C3 and C4) and frontal (averaged across F3 and F4) channels using Welch's method. This utilized a 4-second Hamming window length with 50 % overlap, focussing on frequency bands that are prominent during SWS, that is, slow oscillation (0.3–1 Hz), delta (1–4 Hz), and sigma/spindle (12-15Hz) bands. A MANOVA was used to assess group differences.

As replay during sleep could have potentially caused sleep disruptions, resulting in reduced sleep quality, sleep quality was examined and compared between the three experimental groups. The following measures regarding sleep quality, which have been used in the literature[43,44] were considered: time awake after sleep onset (in minutes), sleep efficiency (TST in percentage of the time from sleep onset until the last wake event), the number of transitions from one sleep stage to another, the transition index (number of transitions per hour of sleep), the number of awakenings (> 15 seconds), the awakening index (number of awakenings per hour of sleep), the number of arousals, and the arousal index (number of arousals per hour of sleep). A MANOVA examined group differences on these variables. To assess more subtle changes in sleep quality related to SWS, the sleep stage in which the replay was presented, the arousal index, the transition index, and the awakening index (number of events per time spent in SWS) for SWS only, were calculated and analyzed with a MANOVA.

RESULTS

Abstraction Performance and Association with Sleep Parameters

Auditory Recall Task

Performance in the auditory recall task served as measure for abstraction, as participants needed some knowledge of the auditory probabilistic pattern to correctly identify new sequences that followed the same pattern. To assess the effect of replay on abstraction performance, we were particularly interested in how the overnight change in performance differed between groups. The results are shown in Figure 3A. A 2 × 3 mixed measures ANOVA with factors session and group revealed no significant main effect of session, $F(1,39) = 0.01$, $p = .93$, no difference between groups, $F(2,39) = 2.21$, $p = .12$, but importantly a significant session × group interaction, $F(2,39) = 5.42$, $p = .01$. While, surprisingly, the SWS-R group showed a significant decrease in performance, at a Bonferroni-corrected α-level of 0.017, (mean S1: 1.13, standard error [SE]: 0.14, mean S2: 0.77, SE: 0.12), $t(13) = 2.80$, $p = .015$, the performance in the control group (mean S1: 1.25, SE: 0.11, mean S2: 1.34, SE: 0.15), $t(13) = 0.74$, $p = .47$, and the PS-R group (mean S1: 1.16, SE: 0.14, mean S2: 1.45, SE: 0.23), $t(13) = 1.68$, $p = .12$, did not change across sessions. As expected, performance between groups did not differ in the immediate recall session, $t(26) \leq 0.65$, $p \geq .52$, indicating that all groups had a comparable performance prior to the consolidation interval. After sleep, in the delayed recall session, the SWS-R group performed significantly worse than the control group, $t(26) = 2.94$, $p = .007$, and the PS-R group, $t(26) = 2.66$, $p = .013$, at a Bonferroni-corrected α-level of 0.017. Performance between control and PS-R group did not differ, $t(26) = 0.41$, $p = .69$. Importantly, performances in each session in each group were significantly greater than chance, $t(13) \geq 6.27$, $p < .001$, demonstrating that participants in all conditions were successful in conducting the task. In summary, against our expectations, these results showed selective overnight performance impairment for the SWS-R group.

To investigate whether the performance impairment in the SWS-R group was driven by over-generalization or lack of abstraction, we also assessed the raw scores of hits, misses, false alarms, and correct rejections with 2 × 3 mixed measures ANOVAs with factors session and group (see Table 1 for the raw performance scores). Over-generalization would be reflected in an increase of false alarms, an increase in misses would suggest impairment in the abstraction of the statistical pattern. However, the results did not show any significant effects on the interaction between session and group (hits: $F = 1.65$, $p = .21$, correct rejections: $F = 0.45$, $p = .64$, misses: $F = 1.00$, $p = .38$, false alarms: $F = 0.76$, $p = .48$) suggesting that over-generalization as well as impaired abstraction may have contributed to the impaired performance in the SWS-R group.

Visual Recall Task

As the visual stimuli in the visual recall task shared no superficial characteristics with the auditory exposure stream, but only coincided with the underlying statistical pattern,[8,11] this task could only be solved by abstracting the probabilistic pattern and generalizing it to the visual modality. Therefore, this task allowed us to measure the effect of replay on cross-modal generalization. The results are shown in Figure 3B. One participant of the SWS-R group did not complete the visual recall task due to a technical failure. A one-way ANOVA revealed a marginally significant difference in performance between the three experimental groups, $F(2,38) = 3.10$, $p = .057$. Planned post hoc comparisons, using a Bonferroni-corrected α-level of 0.025, showed that the SWS-R group performed significantly worse than the control group, $t(25) = 2.49$, $p = .020$, and marginally worse than the PS-R group, $t(25) = 2.25$, $p = .033$. At the group level, performance was above chance for the control group and the PS-R group (Bonferroni-corrected α-level of 0.017), $t(13) \geq 2.88$, $p \leq .013$, demonstrating that they were successful in learning the task. At the individual level, eight participants of the control group and seven participants of the PS-R group performed above chance. Performance of the SWS-R group did not exceed chance level at the group level, $t(12) = 0.79$, $p = .45$, only two participants performed above chance at the individual level. These results are in line with the results of the auditory recall task and showed selective failure of the SWS-R group to transfer knowledge about the statistical structure to the visual domain.

Association Between Overnight Performance Change and SWS

Previous studies using this paradigm showed that the amount of SWS predicted the behavioral performance change from the immediate to the delayed recall session.[7,8] This association was also assessed in the current study. For one participant of the control group, no PSG data were available, due to technical difficulties during the sleep monitoring. Results of the PSG analysis of the remaining participants are presented in Table 2. The control group showed, as expected, a positive correlation between the proportion spend in SWS and the behavioral performance change from immediate to delayed recall, $r(13) = 0.59$, $p = .035$), shown in Figure 4. Participants with a large proportion of SWS showed an overnight improvement in performance, while

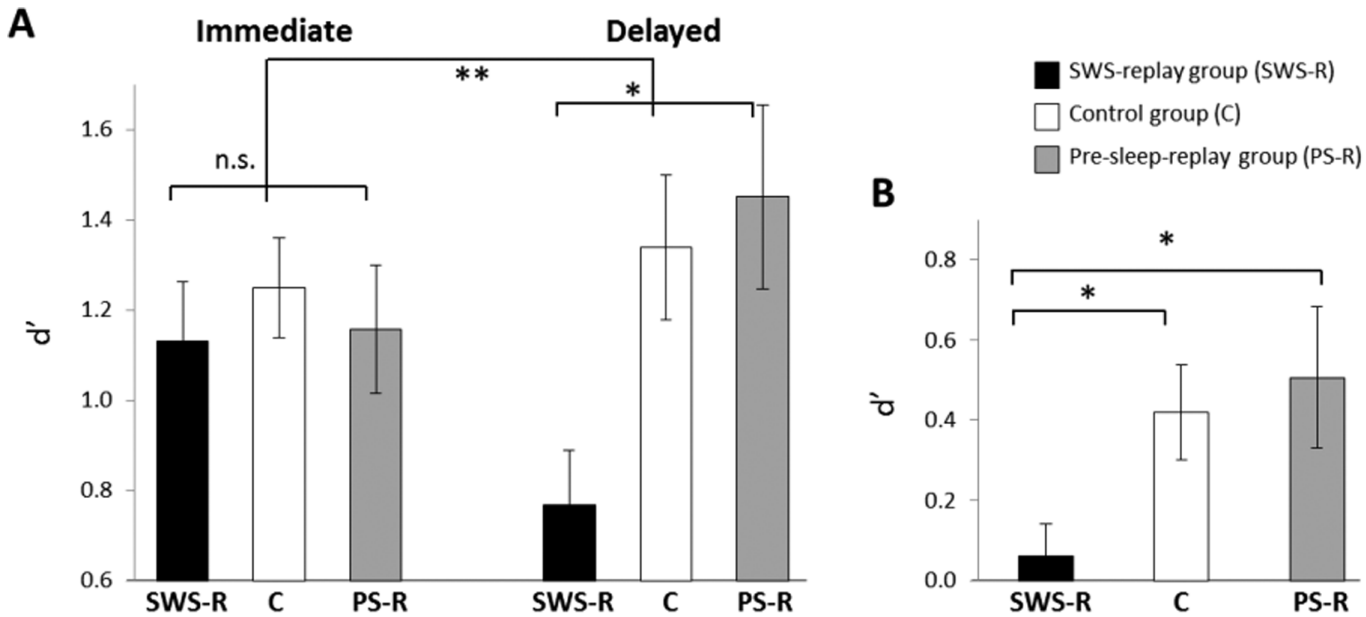

Figure 3—Behavioral results. (A) Auditory recall task. While in the immediate recall session, there was no difference in the performance between groups, in the delayed recall session a difference between the groups emerged (assessed by one-way analysis of variance [ANOVA]). The SWS-replay group showed a significant decrease in correct recognition of structured and unstructured sequences after consolidation, whereas the control group and the presleep-replay group showed no change in performance. This group difference in the performance change across consolidation was significant in a 2 × 3 ANOVA with factors session and group. (B) Visual recall task. The control group and the presleep-replay group exhibited strong performance, while the SWS-replay group performed at chance. The difference in performance between the SWS-replay and the two other groups was significant. $^{**}p < .001$, $^{*}p < .05$, n.s.: $p > .1$.

participants with little SWS showed performance impairment. This correlation was specific to SWS; no other sleep stage (S1, S2, REM, TST) showed a significant correlation, $r(14) \leq 0.11$, $p \geq 0.73$. In the SWS-R group, we found no association between the change in performance and SWS, $r(14) = -0.12$, $p = .67$ or any other sleep stage, $r(14) \leq 0.32$, $p \geq .27$. While sleep-related processing seemed to facilitate the behavioral performance in the control group, our results suggest that TMR disturbed these mechanisms and thereby abolished the beneficial effect of sleep.

The PS-R group showed a strong correlation between SWS and the behavioral performance change, but surprisingly, this association was negative, $r(14) = -0.70$, $p = .005$. Participants with a high proportion of SWS showed a decrease in performance from immediate to delayed recall, while participants with a low proportion of SWS showed an improvement. This correlation was specific to SWS; no other sleep stage showed a significant correlation, $r(14) \leq 0.43$, $p \geq .12$.

Table 1—Raw Performance Scores of the Immediate and Delayed Auditory Statistical Learning Task.

Group	Measurement	Session 1	Session 2	*p*-value
SWS-R	Hits	25.5 ± 0.4	22.1 ± 0.6	.06
	Correct rejections	30.2 ± 0.6	29.6 ± 0.6	.43
	False alarms	10.0 ± 0.4	11.4 ± 0.4	.11
	Misses	18.3 ± 0.4	20.4 ± 0.5	.20
Control	Hits	24.4 ± 0.5	24.1 ± 0.5	.81
	Correct rejections	33.3 ± 0.4	33.5 ± 0.7	.87
	False alarms	8.5 ± 0.4	8.7 ± 0.7	.87
	Misses	17.8 ± 0.5	17.7 ± 0.5	.94
PS-R	Hits	27.0 ± 0.3	25.6 ± 0.5	.23
	Correct rejections	32.6 ± 0.4	33.5 ± 0.6	.51
	False alarms	8.9 ± 0.4	8.1 ± 0.6	.61
	Misses	15.7 ± 0.3	16.0 ± 0.4	.73

Data are means ± SE; 84 items (42 old and 42 new) were presented in each session. *p*-values are from independent samples *t*-tests on the performance score of the two sessions.

No Difference in Sleep Quality Between Groups

One explanation for the observed behavioral interference effect could be that the replay—independent of the cues themselves—disrupted sleep and thereby disrupted sleep-related consolidation processes or impaired sleep quality resulting in a less restorative function of sleep. To investigate this, we compared alertness, sleep structure, and sleep quality between groups.

Alertness

Differences in alertness between the three experimental groups were assessed with one-way ANOVAs on the average scores of the KSS and the SSS for each session. Groups did not differ in both sessions on both scales, $F(2,39) \leq 1.87$, $p \geq .17$, suggesting that there was no difference in alertness between groups in either session. The change in alertness between S1 and S2 did not differ between groups for either the KSS, $F(2,39) = 0.90$, $p = .42$, or the SSS, $F(2,39) = 0.99$, $p = .38$. As differences in alertness could also be reflected by differences in responses times, response times were assessed between the three experimental groups. To account for the fact, that response time is a sensitive measure on the statistical learning paradigm, that is, participants are faster on correct than incorrect trials,[8] a 2×3 ANOVA with factors trial accuracy (levels: correct, false) and group was conducted on response times, separately for each session. Importantly, there was no significant main effect of group (immediate recall: $F(2,39) = 0.21$, $p = .82$; delayed recall: $F(2,39) = 0.64$, $p = .54$) and no significant interaction between group and accuracy (immediate recall: $F(2,39) = 1.40$, $p = .26$; delayed recall: $F(2,39) = 1.82$, $p = .18$) in either session, confirming that all groups had a similar pattern of response times. Together, these results suggest the observed group differences in performance were not due to differences in alertness.

Table 2—Polysomnography Results.

Parameter	SWS-R group	Control group	PS-R group	*p*-value
Total sleep time (minutes)	459 ± 19	433 ± 13	428 ± 14	.34
REM (%)	18.7 ± 1.3	18.7 ± 1.6	19.7 ± 1.1	.83
Stage 1 (%)	6.0 ± 1.1	5.7 ± 0.9	4.5 ± 0.8	.52
Stage 2 (%)	63.7 ± 1.4	61.8 ± 1.5	58.4 ± 1.8	.07
SWS (%)	11.6 ± 1.5	13.8 ± 1.5	17.4 ± 1.4	.03*
Non-REM spindle density	0.77 ± 0.09	0.83 ± 0.10	0.91 ± 0.10	.62

non-REM = nonrapid eye movement sleep (including SWS and stage 2 sleep); PS-R = presleep replay; SWS-R = SWS replay.
Spindle density is measured as number per minute. Data are means ± SE, *p*-values are from one-way ANOVAs.
*Significance at $p = .05$ level.

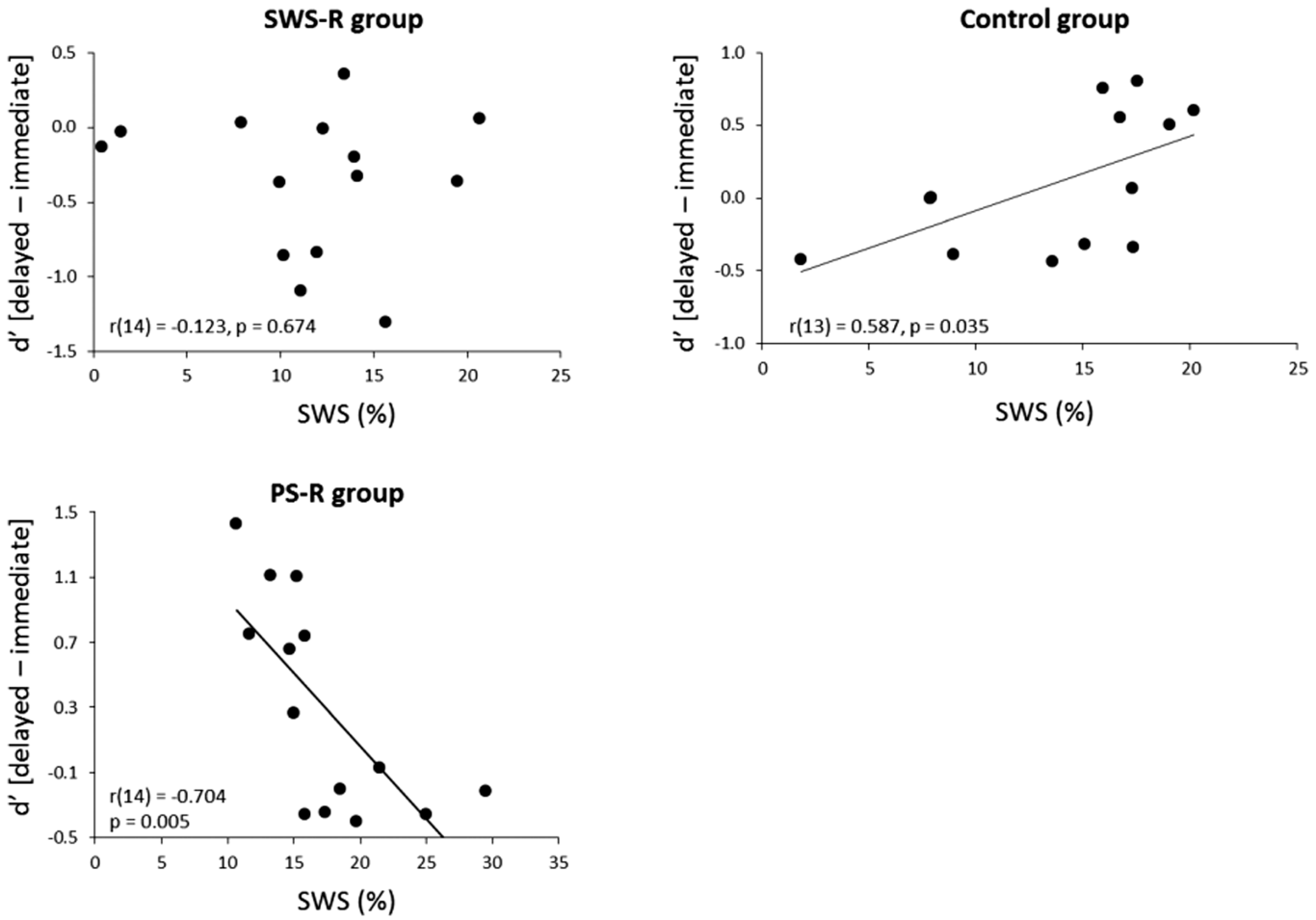

Figure 4—Relationship between slow wave sleep (SWS) and behavioral performance. The SWS-replay (SWS-R) group showed no association between SWS and the overnight performance change. In the control group, the improvement in task performance from the immediate- to the delayed-recall session was significantly correlated with the amount of SWS obtained. The presleep-replay (PS-R) group showed a significant but negative association. Participants with a high proportion of SWS showed a decrease in performance from the immediate- to the delayed-recall session while participants with a low proportion of SWS showed an improvement.

Sleep Structure

A MANOVA on the proportions spent in each sleep stage was used to investigate differences between groups in sleep structure. The analysis showed no significant multivariate effect of group, $F(8,72) = 1.42$, $p = .20$. To assess more subtle differences between groups, univariate F tests were examined for each variable. The results are presented in Table 2. These analyses revealed a significant effect for SWS, $F(2,38) = 4.05$, $p = .025$. This effect was driven by significantly more SWS in the PS-R group compared to the SWS-R group, $t(26) = 2.82$, $p = .009$ and a trend toward more SWS of the PS-R group compared to the control group, $t(25) = 1.78$, $p = .088$. Importantly, however, there was no difference between the SWS-R group and the control group, $t(25) = 1.02$, $p = .32$, suggesting that these two groups were comparable in terms of the amount of SWS they obtained. Univariate analyses also revealed a marginal significant effect for stage 2 sleep (S2), $F(2,38) = 2.92$, $p = .066$. This was driven by significantly more S2 in the SWS-R group compared to the PS-R group, $t(26) = 2.32$, $p = .029$, but again there was no difference between the other groups $t \leq 1.44$, $p \geq .16$.

To investigate more subtle differences specific to SWS, the sleep stage in which the replay took place, we assessed with a MANOVA differences in the power spectral density of SWS, in slow oscillation, delta and spindle frequency bands of central and frontal electrodes. The results are presented in Table 3. The multivariate group effect was not significant, $F(12,68) = 1.09$, $p = .38$. Planned univariate F tests on all dependent variables also showed no differences between groups, $F(2,38) \leq 2.05$, $p \geq .14$. In summary, these results suggest that the observed differences in abstraction performance between groups were not due to either differences in the overall sleep structure or SWS-specific structural changes caused by the replay.

Sleep Quality

As replay during sleep could potentially disrupt sleep and impair sleep quality, which could explain the observed performance decrease in the SWS-R group, sleep quality was assessed with respect to awakenings, arousals, and sleep-stage transitions. The results are summarized in Table 4. A MANOVA was used to examine group differences. The multivariate effect of group was

not significant, $F(16,64) = 0.99$, $p = .48$. To assess more subtle differences between groups, univariate F tests were examined for each variable, however, none of the variables showed a significant effect, $F \leq 1.86$, $p \geq .17$ Furthermore, mean occipital alpha power during non-REM sleep, which can be an indicator of arousal or brief awakenings,[32] was also assessed but did not differ between groups (SWS-R: 3.43 ± 0.42 μV^2/Hz, PS-R: 3.74 ± 0.31 μV^2/Hz, control: 4.73 ± 0.55 μV^2/Hz; $F(2,38) = 2.31$, $p = .11$). In summary, sleep quality did not differ between groups, and it is therefore unlikely differences in sleep quality explain the performance impairment of the SWS-R group. Since replay was presented during SWS in the SWS-R group and hence might have affected this sleep stage in particular, we also examined sleep quality of SWS only. A MANOVA was used on the following dependent variables: SWS transition index, SWS awakening index, and SWS arousal index. Results are presented in Table 5. The multivariate group effect was not significant, $F(6,74) = 1.75$, $p = .12$. Planned univariate F tests on the dependent variables revealed a significant group difference in the SWS arousal index, $F(2,38) = 0.64$, $p = .039$, driven by a marginal significantly higher arousal index for the control group compared to the SWS-R group ($t(25) = 2.00$, $p = .056$) and the PS-R group ($t = 2.01$, $p = .055$). The SWS arousal index did not differ between the SWS-R group and the PS-R group, $t(26) = 0.19$, $p = .85$.

Overall, none of the measures that we used to explore differences in alertness, sleep structure, and sleep quality showed a negative effect of replay. Hence, our findings suggest that the abstraction impairment of the SWS-R group was unlikely to be due to mechanical disruption of sleep but due to mechanistic interference of the replay cues with sleep-dependent memory processing.

Details of the Replay

In the SWS-R group, the replay was stopped immediately when participants left SWS or showed signs of an arousal. On average, the replay was stopped 1.7 ± 0.1 (SE) times per participant (minimum: 0 times, maximum: 4 times). For one participant of the SWS-R group, the six replay fragments were only played once.

N-Back Task

Data from one participant of the control group were lost due to a technical failure. A 3 × 6 mixed measures ANOVA was used to assess differences in performance on the two-back task between experimental groups. Importantly, we observed no difference between groups, $F(2,38) = 1.80$, $p = .18$ or group × round interaction, $F(10,190) = 1.35$, $p = .21$. The main effect of round was significant, $F(5,190) = 6.70$, $p \leq .001$, with

Table 3—Power Spectral Density (μV^2/Hz) During Slow Wave Sleep.

	Frequency band	SWS-R group	Control group	PS-R group	*p*-value
Central	Slow oscillation (0.3–1 Hz)	989 ± 113	871 ± 101	1139 ± 128	.28
	Delta (1–4 Hz)	201 ± 25	228 ± 26	272 ± 37	.24
	Sigma (12–15 Hz)	2.46 ± 0.42	3.13 ± 0.52	3.07 ± 0.46	.55
Frontal	Slow oscillation (0.3–1 Hz)	1043 ± 104	952 ± 107	1276 ± 133	.14
	Delta (1–4 Hz)	265 ± 34	301 ± 35	386 ± 66	.20
	Sigma (12–15 Hz)	2.59 ± 0.54	3.57 ± 0.61	3.45 ± 0.57	.43

PS-R = presleep replay; SWS-R = SWS replay. Data are means ± SE. *p*-values are from one-way ANOVAs.

Table 4—Overall Sleep Quality.

Parameter	SWS-R group	Control group	PS-R group	*p*-value
Time awake after sleep onset (minutes)	28.2 ± 4.2	33.1 ± 6.0	40.9 ± 10.7	.49
Sleep efficiency (%)	94.3 ± 0.7	92.9 ± 1.3	91.6 ± 2.1	.44
No. transitions	94.1 ± 8.0	100.9 ± 12.9	75.9 ± 6.9	.17
Transition index	11.7 ± 1.0	12.9 ± 1.6	9.8 ± 0.9	.17
No. awakenings	12.9 ± 1.7	17.2 ± 4.1	11.6 ± 1.5	.30
Awakening index	1.67 ± 0.19	2.42 ± 0.59	1.63 ± 0.22	.26
No. of arousals	81.1 ± 12.5	91.5 ± 8.2	76.9 ± 5.8	.53
Arousal index	10.7 ± 1.8	12.7 ± 1.1	10.8 ± 0.8	.48

Index = number of events per hour of sleep; PS-R = presleep replay; SWS-R = SWS replay; sleep efficiency = (time awake)/(sleep period) × 100. Data are means ± SE. *p*-values are from one-way ANOVAs.

Table 5—Sleep Quality of Slow Wave Sleep.

Parameter	SWS-R group	Control group	PS-R group	*p*-value
SWS transition index	0.35 ± 0.08	0.41 ± 0.10	0.22 ± 0.04	.17
SWS awakening index	0.012 ± 0.004	0.010 ± 0.007	0.010 ± 0.004	.96
SWS arousal index	0.054 ± 0.011	0.104 ± 0.025	0.053 ± 0.008	.04*

PS-R = presleep-replay; SWS index = number of events during SWS divided by the total amount of SWS (in min); SWS-R = SWS replay. Data are means ± SE. *p*-values are from one-way ANOVAs.
*Significance at $p = .05$ level.

increasing performance across rounds. These results suggest that the PS-R group was not distracted by the presentation of the replay stream and focused on the two-back task.

DISCUSSION

In the current study, we explored whether TMR during SWS further enhances the beneficial effect of sleep on the extraction of statistical regularities in an auditory statistical learning paradigm. Surprisingly, we found that the beneficial effect of sleep on abstraction was abolished when the probabilistic auditory sequence was replayed during SWS. While the overnight performance change in the detection of structured and unstructured auditory sequences was positively correlated with the amount of SWS in the control group, the group that received the replay during SWS showed no such association and performance was impaired after sleep. This negative effect on task performance was specific to the replay during SWS. Therefore, these results suggest that sleep-dependent mechanisms, which mediate the abstraction of the underlying statistical pattern, were disrupted.

That sleep facilitates processes of abstraction and generalization has been observed in a range of different tasks involving verbal concepts,[6] probabilistic rules,[3] number sequences,[4] and grammar learning in infants.[45] The beneficial effect of sleep on the extraction of auditory probabilistic sequences used in the current task was established by Durrant et al.[7,8,11] They consistently reported that abstraction performance in this task improved after sleep and that the level of improvement was predicted by the amount of SWS obtained.[7,8,11] Although we did not observe a performance improvement across sleep in any group, we replicated the association between SWS and performance change in the control group. In line with the previous studies, participants with a high proportion of SWS showed an improvement in performance across sleep, while participants with a low proportion of SWS showed impairment. These findings support the hypothesis that processes during SWS mediate the abstraction of statistical regularities.

The benefit of sleep on memory consolidation and reorganization has been attributed to repeated reactivation of memory traces during SWS, driven by the hippocampus.[19,21,46–49] Memory reactivations during SWS occur in temporal relationship with hippocampal sharp wave ripples and are thought to be orchestrated with the occurrence of thalamocortical spindles by the up-phases of slow oscillations.[17,46,50] This temporal synchrony between memory reactivation and increased neocortical receptivity, induced by spindles, may enable hippocampal-neocortical information exchange and memory reorganization.[23] Functional imaging results from Durrant et al.[8] suggest that the underlying mechanisms of abstraction in the current task indeed involve SWS-mediated reorganization of the brain circuits that support memory. Specifically, Durrant et al.[8] demonstrated that the overnight performance change was associated with a gradual shift from the hippocampal to the striatal memory system and that this change in the underlying neural substrates was predicted by the amount of nocturnal SWS. One hypothesis is that such sleep-related enhancements of abstraction and generalization result from the recurrent reactivation of memory elements that are shared between individual item memories.[16,51] By strengthening the overlapping connections between separate memories, the "gist" emerges that enables generalization to new stimuli or situations.[16,51] Based on this theory, we hypothesized that TMR would, by manipulating the occurrence of spontaneous reactivations,[28] promote the abstraction process through a selective enhancement of the highly likely transitions. Surprisingly, however, we observed the opposite: TMR impaired task performance for both auditory and visual versions of the task and abolished the association with SWS. These findings suggest that representing the probabilistic sequence during SWS interfered with sleep-dependent memory processing.

The auditory recall task can be solved either by abstracting transition statistics (ie, the probabilistic sequence) or by using episodic memory of concrete fragments of the exposure sequence.[8,52,53] The visual recall task, however, can only be solved by applying knowledge about the probabilistic structure as the visual stimuli share no superficial characteristics with the auditory exposure stream. They only coincide with the underlying statistical pattern.[8,11] Thus, presenting the stimuli in a different modality at testing ensured that explicit episodic memory for fragments could not aid test performance and extraction of the underlying probabilistic pattern was necessary. Importantly, we found that the replay-driven overnight impairment was also present in the visual recall task. While participants of the control and PS-R group performed well above chance in this task, clearly demonstrating some knowledge of the statistical structure, performance of the replay group was at chance level. Hence, the current findings suggest that the replay of the exposure stream interfered with the abstraction process and did not just impair episodic memory. From our study, no conclusion can be drawn in terms of the underlying mechanisms. We can only speculate that the probabilistic nature of the replay cue caused this interference. As we used the probabilistic sequence as memory cue during SWS, which is highly variable, the cue and the stored memory representations

of the concrete fragments did not perfectly overlap. Therefore, the spontaneous reactivation of the concrete fragments might have been disrupted by the presentation of the partially overlapping memory cues, resulting in impaired performance and lack of association with SWS. Even though this is speculative, it raises important questions about the nature of TMR-cued reactivation. So far, in all studies that successfully applied TMR to enhance the sleep benefit on memory stabilization, only perfectly matching stimuli were used as reactivation cues. Cousins et al.,[31,35] for example, used a fixed (not probabilistically determined) auditory sequence as memory cue during SWS (in the same sleep laboratory with the same set up in terms of volume, background noise, and replay procedure as the current study) and found enhanced sequence knowledge after sleep. A recent study by Batterink et al.,[37] which provided the first evidence that TMR can manipulate grammatical generalization during sleep, also used memory cues that did not vary probabilistically. Based on these results, the question arises whether partially overlapping memory cues might have the potential to disrupt the beneficial effect of sleep on memory reorganization.

Another explanation might be that due to the length of the replay fragments, processes necessary for stabilizing reactivated memory traces were disrupted. A recent study by Schreiner et al.[54] showed that presenting additional auditory input within a period of 1500 ms after a memory cue completely blocked the beneficial effect of cueing during sleep on later recall. They suggested that during this sensitive period additional input disrupted neural and oscillatory processes critical for memory stabilization after reactivation during sleep. As in the current study, cues were presented in long blocks interfering effects might have occurred during these sensitive phases and blocked sleep-dependent processing as suggested by Schreiner et al.[54]

In the current study, the replay-related performance impairment was specific to the replay during sleep. The group who received the replay during wakefulness, directly before sleep, showed comparable performance to the control group. Surprisingly, however, the replay before sleep also had an interfering effect and reversed the association with SWS. Participants with a low proportion of SWS showed an overnight improvement in performance while participants with a high proportion of SWS got worse. These results may indicate that SWS in this group was associated with the consolidation of the wrong thing, such as for example unnecessary details like low probability transitions. As participants in this group received another presentation round of the exposure stream after the test phase, it is likely that they perceived the exposure stream differently and focused on other aspects compared to the initial encoding. Why this causes impairment, remains unclear. However, it is possible that it disrupted an abstraction process which had already begun after the initial training session. This group also showed a slight difference in the sleep structure with a higher proportion of SWS than the two other groups, which might also suggest that some different processes occurred. Importantly, however, participants performed well above chance in the visual recall task and showed, unlike the group who received the replay during SWS, no impairment in the auditory recall task, indicating that this group had abstracted the underlying statistical structure. Therefore, the catastrophic interference with the abstraction of the underlying statistical structure was specific to the replay during SWS.

In terms of limitations, we cannot exclude the possibility that the two-back task caused a nonspecific interference effect, which might explain the lack of overnight performance improvement in the control group that was reported in previous studies.[7,8] As the two-back task was performed by all experimental groups, it is, however, unlikely that this led to the observed differences between the groups or the unexpected behavior of the PS-R group. We should also note that, while the sample size of $N = 14$ is in line with prior studies of how sleep interacts with this statistical learning paradigm[7,8,11] as well as the bulk of the literature on TMR using auditory cues,[32,55–58] a greater sample size may nevertheless have provided additional confidence in the results. Hence, due to the small sample size of the experimental groups the results have to be interpreted with caution.

Another limitation is the between-subject design. The observed negative effect of the replay on task performance could also be explained by a mechanical disruption of sleep independent of the memory cue itself, leading to a disruption of sleep-dependent consolidation processes. However, this is unlikely, since general sleep and SWS parameters, such as SWS amount, spectral power of frequency bands that are dominant during SWS, and SWS quality measures did not differ between the SWS-R group and the control group. Another possibility is that the replay caused a general impairment of sleep quality resulting in a less restorative function of sleep and increased tiredness, which could theoretically explain the impaired performance of the replay group. However, comparable sleep quality and alertness measures between groups suggest that it is highly unlikely that the replay impaired sleep quality and that differences in performance were due to differences in alertness. Overall, our findings suggest that the replay-related impairment was caused through a specific interference with the consolidation process and not through a mechanical disruption of sleep.

In conclusion, the current results suggest that representing the probabilistic auditory sequence during SWS interfered with the abstraction process and therefore impaired subsequent performance in both auditory and visual recall tasks. These findings raise important questions about the scope and the underlying mechanisms of cued memory reactivation, which need to be addressed in further studies.

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FUNDING

This work was supported by the Biotechnology and Biological Sciences Research Council: grant [BB/F01760X/1] and by the University of Manchester.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2017
Submitted in final revised form April, 2017
Accepted for publication July, 2017
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DISCLOSURE STATEMENT

None declared.