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SLEEP COGNITION AND BEHAVIOR

The Benefits of Targeted Memory Reactivation for Consolidation in Sleep are Contingent on Memory Accuracy and Direct Cue-Memory Associations

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Study Objectives: To investigate how the effects of targeted memory reactivation (TMR) are influenced by memory accuracy prior to sleep and the presence or absence of direct cue-memory associations.

Methods: 30 participants associated each of 50 pictures with an unrelated word and then with a screen location in two separate tasks. During picture-location training, each picture was also presented with a semantically related sound. The sounds were therefore directly associated with the picture locations but indirectly associated with the words. During a subsequent nap, half of the sounds were replayed in slow wave sleep (SWS). The effect of TMR on memory for the picture locations (direct cue-memory associations) and picture-word pairs (indirect cue-memory associations) was then examined.

Results: TMR reduced overall memory decay for recall of picture locations. Further analyses revealed a benefit of TMR for picture locations recalled with a low degree of accuracy prior to sleep, but not those recalled with a high degree of accuracy. The benefit of TMR for low accuracy memories was predicted by time spent in SWS. There was no benefit of TMR for memory of the picture-word pairs, irrespective of memory accuracy prior to sleep.

Conclusions: TMR provides the greatest benefit to memories recalled with a low degree of accuracy prior to sleep. The memory benefits of TMR may also be contingent on direct cue-memory associations.

Keywords: consolidation, memory, reactivation, slow wave sleep

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Significance

Research has demonstrated that memory reactivations in the sleeping brain can be triggered by re-exposing individuals in slow-wave sleep to sound cues previously associated with the newly-learned materials; a technique known as targeted memory reactivation (TMR). In this study, we examined how the success of TMR is influenced by (1) the presence or absence of direct cue-memory associations and (2) the accuracy with which newly-learned memories are recalled prior to sleep. Our findings suggest that low accuracy memories are more responsive to TMR and that the benefits of TMR for consolidation are contingent on the presence of direct cue-memory associations. These data have important implications for the potential educational applications of TMR.

INTRODUCTION

There is now a wealth of behavioral and physiological evidence in favor of the view that memory consolidation is supported by sleep.[1–3] Beyond merely sheltering memories from the interference posed by wakefulness, recent work has indicated that the sleeping brain actively facilitates memory processing and, thereby, instills qualitative changes to representations encoded throughout the preceding day.[4,5] According to the active systems model of consolidation,[4,6] sleep dependent memory processes are underpinned by a covert reactivation of newly formed representations during slow wave sleep (SWS), as indexed by spontaneous neural activity in the brain regions employed at learning, such as the hippocampus and neocortex. Driven by the electroencephalography (EEG) slow oscillations (< 1 Hz) and sleep spindles (~12–15 Hz) that characterize SWS, these memory reactivations are thought to mediate the processes of stabilisation and integration that underpin long-term memory storage. In support of this view, research with both animals and humans has shown that patterns of neural activity observed during learning are "replayed" during SWS, with the extent of such neural replay often predicting subsequent task performance.[7–12]

The development of a technique known as targeted memory reactivation (TMR) in recent years has provided a method for cuing the reactivation of specific memories in SWS.[13–15] In a typical TMR experiment, participants form a number of new memories (e.g., for the screen locations of different pictures) that are each associated with a semantically related sound (e.g. a picture of a cat and a "meow" sound) before a period of sleep in which a subset of the sounds are replayed during SWS. Memories associated with the replayed sounds are typically recalled with higher accuracy than those associated with the nonreplayed sounds, indicating that TMR has a beneficial influence on consolidation. Notably, earlier work has also revealed similar benefits of re-exposing individuals to olfactory memory cues in SWS,[16–19] but the current study focuses on acoustic cues.

Whereas TMR provides a unique and unobtrusive means of influencing memory consolidation in the sleeping brain, our knowledge of how the processes underpinning TMR correspond to those outlined in existing models of hippocampal replay is somewhat limited. Despite recent work indicating that the effects of TMR are influenced, for example, by the emotionality of newly learned materials[20] or the structural integrity of the hippocampus,[21] the factors that are pertinent to the success of TMR for consolidation are not well understood. By placing greater attention on such factors in experimental research, it may be possible to identify methods for optimizing the memory-enhancing effects of TMR. Such an approach would also provide invaluable insights to the mechanisms of TMR and broaden our understanding of both memory consolidation and auditory processing during sleep.

Prior studies of auditory TMR have only included sounds cues that are presented, and therefore encoded, at the same time

as each memory (i.e. direct cue-memory associations).[13–15,20–22] It is therefore unknown whether the success of TMR is contingent on direct cue-memory associations, or whether acoustic cues indirectly linked to the newly formed memories can also facilitate sleep dependent consolidation. Sleep has been shown to not only benefit memory stabilization,[23,24] but also support relational memory, the flexible ability to generalize across existing stores of memory information.[25] Accordingly, if a sound cue is directly associated with a particular memory, which is linked to additional memory information encoded at another time, then TMR may enhance the consolidation of all associated memory components via relational memory strengthening.

Another factor that may influence the success of TMR is the strength of newly encoded memories. Previous work has suggested that endogenous offline consolidation processes are modulated by pre-sleep retention levels, although different experimental approaches have made it difficult to draw any general conclusions on the nature of such effects. In one study, sleep facilitated the recall of word pairs memorized to a pre-sleep criterion of 60% correct, but not 90% correct,[26] whereas another showed a benefit of sleep for three declarative memory tasks, but only in individuals who had strongly acquired the tasks prior to sleep.[27] More recent work provided the first investigation of how learning levels prior to sleep influence the success of TMR, suggesting that TMR most effectively supports consolidation when memories are neither too strong nor too weak.[13] Further work on this topic is necessary to elucidate the effect of pre-sleep memory accuracy on the consolidation benefits of TMR, and thereby further our understanding of the mechanisms underlying this technique.

The memory effects of TMR have been linked to both the time spent in SWS and the related occurrence of sleep spindles,[20,21,28,29] suggesting that these sleep parameters are critical for memory reactivations to take place. However, the precise manner in which SWS and spindles influence memories that are cued by TMR is currently unclear. Recent work has suggested that, rather than boosting the consolidation of reactivated memories instantaneously, TMR initiates an enhanced consolidation process during subsequent SWS that is mediated by sleep spindles,[20] but further evidence is required to substantiate this view. Moreover, the differential effects of SWS on reactivated and nonreactivated memories following TMR have yet to be investigated.

In the current study, we investigated how the success of TMR is influenced by (1) the presence or absence of direct cue-memory associations and (2) the accuracy with which newly-learned memories are recalled prior to sleep. Using an established TMR paradigm,[13–15,22] participants were trained to associate each of 50 pictures with a different location on a computer screen while hearing a semantically related sound, and then took a nap during which half of the sounds were replayed in SWS. Importantly, prior to the picture-location task, participants were also trained to associate each of the 50 pictures with an unrelated, visually presented word, but no sounds were played. Accordingly, each of the acoustic cues delivered in SWS was directly linked to a picture location, but also indirectly linked to a word that was previously associated with the picture. Performance in pre-sleep tests provided a means of quantifying how the benefits of TMR for picture-location and picture-word recall were influenced by memory accuracy prior to sleep. Moreover, via sleep monitoring with polysomnography (PSG), it was possible to investigate whether the benefits of TMR for consolidation were mediated by SWS and associated sleep spindles.

METHODS

Participants

Fifty-one healthy participants aged 18–29 y were recruited for this study. However, 21 of these participants were excluded for the following reasons: inability to reach SWS during the nap phase (8), awakening during sound replay (12), and computer malfunction (1). This left analysis of data from the remaining 30 participants (14 males) aged 18–27 y (mean ± standard deviation [SD] age, 19.87 ± 1.94 y). Undergraduate students on the BSc Psychology program took part in return for course credit whereas other participants were paid £20. Pre-study screening questionnaires indicated that participants had no history of sleep, psychiatric, or neurological disorders, were not using any psychologically active medications, had not consumed alcohol or caffeine during the 24 h that preceded the study, and were nonsmokers. As evaluated with the Pittsburgh Sleep Quality Index[30] all participants had obtained a normal pattern of sleep during the month preceding the study. Written informed consent was obtained from all participants in line with the Research Ethics Committee of the Department of Psychology, University of York.

Stimuli

Pictures and Words

Fifty color photographs depicting everyday living or inanimate objects, or scenes (e.g., a cat, a piano, or a railway line) were adopted from prior studies of auditory TMR.[14,15] Fifty words were extracted from an adapted version of The University of South Florida (USF) word association, rhyme, and word fragment norms[31,32] and consisted of 29 monosyllables, 19 disyllables, and 2 trisyllables. Most words had a high USF concreteness rating (mean ± SD, 5.93 ± 0.32); example words are "lemon", "brick" and "pupil." Mean word length was 5.08 (SD ± 1.01) letters. Each picture was paired with a word for the picture-word pairs task (see next paragraphs). Care was taken to ensure that no obvious semantic relationships existed between any of the pictures or words used in this study.

Sounds

Fifty sounds ranging from 200–569 msec in length (mean ± SD, 460.76 ± 67.03 msec), which were each semantically related to one of the pictures, were adopted from prior studies of auditory TMR[14,15] and the internet (www.freesound.org). An additional sound (guitar strum, 524 msec) was taken from Rudoy et al.[15] for use as a control stimulus during sound replay.

Procedure

Experimental procedures and tasks are illustrated in Figure 1. The experiment began at 13:00 (± 30 min) and was carried out

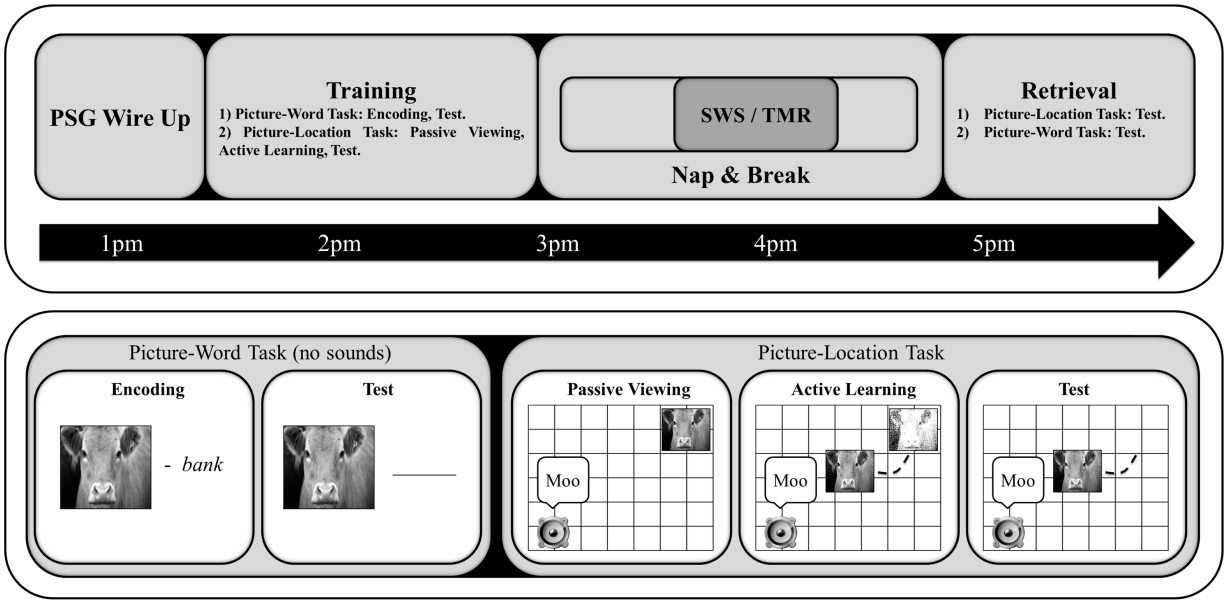

Figure 1—Experimental procedures (top) and tasks (bottom) used in this study. Targeted memory reactivation (TMR) occurred throughout slow wave sleep (SWS). The lightened image in Active Learning represents picture-location feedback. PSG, polysomnography.

in the Sleep, Language and Memory Laboratory, Department of Psychology, University of York, UK. Two experimental sessions (training and retrieval) were separated by a ~90 min nap opportunity. Participants were informed that they were taking part in a study of memory and sleep, but were unaware that TMR would be used during the nap phase. Before the first session began, participants recorded bed and wake times for the most recent sleep period, together with subjective estimations of hours slept in a typical night. Electrodes were then attached to each participant's scalp and face such that sleep could be monitored with PSG. A detachable electrode board was removed from the main PSG system and fastened across the participant's chest, enabling them to move around the laboratory with the electrodes in place. Immediately before the training phase, participants recorded their subjective alertness levels using the Stanford Sleepiness Scale.[33]

Training: Picture-Word Pairs

Participants encoded 50 picture-word pairs. For each randomized trial, a fixation cross appeared in the center of the computer screen for 1.5 sec before it was replaced by one of the picture-word pairs, which remained on the screen for 5 sec until the next trial began. No sounds were played during this task. Participants were instructed to memorize each picture-word pair for a future memory test. To assist encoding, participants received the following instruction: "For each picture-word pair, you should try to form a mental image that involves the picture and the word interacting. For example, if a picture of a tiger appeared with the word 'shoe' you might imagine a tiger wearing a shoe." Each picture-word pair was seen only once during the encoding phase.

Immediately after encoding, participants began a test phase with cued recall. For each randomized trial, a fixation cross appeared in the left center of the screen while an empty rectangular box appeared in the right center of the screen. After 1.5 sec, the fixation cross was replaced by one of the encoded pictures and participants were required to type the associated word into the box and press the "Enter" key within 12 sec. If a correct response was provided within the time limit participants were presented with the word "correct" in blue font. If an incorrect response was provided (including target words with incorrect spelling), or the time limit was surpassed, participants were presented with the word "incorrect" in red font together with a reminder of what the correct answer was (i.e. the correct word is shoe). The feedback screen was displayed for 3.5 sec before the next trial began. As at encoding, no sounds were played in this task. In accordance with prior work on sleep and verbal paired associates learning,[34–37] participants were required to reach a performance criterion of 60% correct responses. The cued recall test was repeated (without additional encoding rounds) until this criterion was met. The mean number of test rounds required to reach the criterion was 1.29 (SD ± 0.46). Pre-sleep performance was defined as the recall score in the last round of testing (i.e., the test round in which the criterion was reached).

Training: Picture Locations

The visuospatial memory task of Rudoy et al.[15] was employed for picture-location training in this study. The task was partitioned into three phases: "passive viewing," "active learning" and "test." For each randomized trial of the passive viewing phase, one of the 50 pictures from the picture-word task was presented in a screen location that was randomly determined for each participant. The picture could appear anywhere on the screen, although a grid background was provided for reference. The sound associated with each picture was played concurrent with the onset of its presentation. Each picture was presented for 3 sec and followed by a 1-sec interval before the next trial

began. Participants were instructed to memorize each of the picture locations for a subsequent test, but were not given any specific instruction regarding memory for the sounds. On account of this procedure, each sound became directly associated with a picture, and thus indirectly linked to the word associated with that picture in the previous picture-word task.

Participants then began the active learning phase, which involved multiple rounds of training. The first two rounds consisted of 50 randomized trials. For each trial, one of the 50 pictures was presented in the center of the screen concurrent with the replay of its associated sound. The prompt "where?" appeared underneath the picture and participants were required to move the picture, using the mouse, to the correct screen location (i.e., the location that it had appeared during the passive viewing phase). Mouse movements elicited picture movement automatically (i.e., no mouse button press was required to "drag and drop" the picture); thus, upon reaching the desired screen-location, participants clicked the left mouse button to finalize their response (no time limit). The picture then "jumped" to reappear in the correct screen location concurrent with an additional replay of its associated sound, and was displayed for an additional 3 sec. Hence, on each trial, participants were able to re-encode the correct location of the picture as well as the acoustic cue. After the first two rounds, the pictures that had been consecutively placed < 4.8 cm (150 screen pixels) from their correct screen location were dropped from the task and active learning continued for the pictures that remained. The remaining pictures continued to be dropped from the task as they were also placed < 4.8 cm from their correct location in two consecutive rounds. Active learning was completed when this criterion was reached for all 50 pictures. The mean number of active learning rounds required to reach the criterion was 9.00 (SD ± 2.60) and the mean number of repetitions per picture was 4.05 (SD ± 1.19). The commencement of each active learning round was self-paced by participants, who were advised that they may take short (~1 min) breaks between rounds as required.

Participants began the test phase immediately after completing active learning. The test was akin to one round of active learning for all 50 pictures, except that participants moved immediately to the next trial after making each response (i.e., instead of the picture re-appearing in its correct location). Responses on the test provided an index of pre-sleep picture-location recall accuracy.

Nap

The electrode board was then reattached to the main PSG system and participants were asked to get into bed and move into a supine position ready for sleep. The sounds that would be used for TMR were then selected via a computerized algorithm that ensured the replayed and nonreplayed sound sets were approximately matched in terms of picture-word recall and picture-location accuracy prior to sleep. The bedroom lights were switched off at 14:30 (± 30 min) and participants were left to sleep. Sound replay (TMR) was initiated after participants had exhibited ~2 min of SWS (as determined via online PSG monitoring). The sound set consisted of 25 study sounds and 25 occurrences of a single control sound (guitar strum) in random order. To help ensure that participants would not be awoken by the experimental stimuli, three additional instances of the control stimulus were placed at the beginning of each sound replay round. The stimulation rate was one sound per 5 sec and the total stimulation time was ~4 min 15 sec. To maximize the potential effect of TMR, the sound set was repeatedly replayed throughout SWS, with a 1-min interval placed between each repetition.[14] The mean number of sound set replays was 3.83 (SD ± 1.76). The sounds were immediately stopped if PSG recordings showed signs of microarousal or awakening, but restarted from the beginning if participants returned to SWS. The nap opportunity ended after ~90 min. Participants were only awoken from sleep stages I or II and never from SWS or rapid eye movement (REM) sleep. To attenuate sleep inertia, participants took a ~20 min break after the nap, during which the PSG electrodes were removed.

Retrieval

Participants completed the Stanford Sleepiness Scale[33] for a second time before repeating the test phase of the picture-location task. The picture-word cued recall test was then also repeated, but no correct/incorrect word feedback was provided on this occasion.

Sound Discrimination

Participants were informed of the true purpose of the experiment and asked whether they had been aware of any sound replay during sleep. Participants then completed a final sound discrimination task in which they were represented with each of the 50 study sounds in random order and, for each, asked to indicate whether they thought it belonged to the replayed sound set (left mouse button click) or the nonreplayed sound set (right mouse button click).

Sound-Word Association Task

To ensure that participants had been able to form indirect associations between the picture-word pairs and the sound cues, we carried out an additional experiment with a separate group of participants (n = 14, five males) aged 18–30 y (mean ± SD age, 20.50 ± 2.95 y). Participants completed the same training procedures as in the main experiment (i.e., picture-word training and then picture-location training) before an additional sound-word association task. Here, participants were presented with the 50 sounds one after another and, for each, asked to recall the relevant word (i.e., the word paired with the picture for which that sound was associated) within 15 sec. Importantly, participants were able to recall the correct word on the majority of trials (mean ± standard error of the mean [SEM], 76.71 ± 2.81%), indicating that indirect associations between the two tasks had been formed.

Equipment

Experimental Tasks

The picture-word and sound-word association tasks were implemented on a personal computer with E-Prime version 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, USA), whereas the picture-location and sound discrimination tasks

were implemented with Presentation version 17.0 (Neurobehavioral Systems, Inc., Berkeley, CA, USA). During the relevant tasks, sounds were heard through headphones (Beyerdynamic DT 234 PRO, Heilbronn, Germany). Visual stimuli were presented ~0.5 m from participants on a 27" flat screen monitor (resolution = 1,920 × 1,080 pixels) positioned at eye level.

Sound Replay (TMR)

Sound replay in sleep was implemented with Presentation version 17.0 (Neurobehavioral Systems, Inc.). Sounds were played via a speaker mounted ~1.5 m above the bed, which was connected to an amplifier in a separate room. To habituate participants to auditory stimulation during sleep, and thus reduce the risk of arousals or awakenings during sound replay, low- intensity white noise was played into the bedroom for the entirety of the nap phase. To promote acoustic clarity, white noise volume was lowered during the replay of each sound such that overall sound intensity remained at ~39 dB.

PSG and Sleep Scoring

A PSG system (Embla Systems N7000, Broomfield, CO, USA) with RemLogic version 1.1 software was used to monitor sleep during the nap phase. After the scalp was cleaned with NuPrep exfoliating agent (Weave and Company, Aurora, CO, USA), gold plated electrodes were attached using EC2 electrode cream (Grass Technologies, Middleton, WI, USA). EEG scalp electrodes were attached according to the international 10-20 system at six standardized locations: central (C3 and C4), occipital (O1 and O2) and frontal (F3 and F4), and each was referenced to an electrode on the contralateral mastoid (A1 or A2). Left and right electrooculography electrodes were attached, as were electromyography electrodes at the mentalis and submentalis bilaterally, and a ground electrode was attached to the forehead. Each electrode had a connection impedance of < 5 kΩ and all signals were digitally sampled at 200 Hz.

For the purposes of detecting SWS in real time, online sleep scoring was conducted on the referenced central electrodes (C3-A2 and C4-A1). To check that sound replay had been initiated in SWS, PSG recordings were subsequently partitioned into 30-sec epochs and scored offline to the criteria of the American Academy of Sleep Medicine.[38] This revealed that one participant had not sustained SWS during the nap, meaning that sound replay had only occurred in sleep stage II. Because the slow oscillations that characterize SWS also occur in stage II sleep, particularly in the early cycles of sleep, we retained this participant in our analyses.[15] Across all participants, 93.0% of sound set replays were judged to have commenced in SWS, whereas the remaining 7.0% began in late stage II sleep. Scored sleep data were partitioned according to the percentage of total sleep time spent in sleep stage I, stage II, SWS, and REM sleep.

Sleep Spindles

PSG epochs scored as either stage II or SWS were extracted from all six EEG channels for spindle analysis. Artefacts were then rejected from the data using EEGLAB version 10.0 (Swartz Center for Computational Neuroscience, University of California San Diego) before a linear finite impulse response filter was used to bandpass filter each channel at 13.5–15 Hz (fast spindles) and 12–13.5 Hz (slow spindles). An automated detection algorithm[39] counted discrete spindle events as amplitude fluctuations within the filtered time series that exceeded a threshold of eight times the mean channel amplitude. Fast and slow spindle density (counts per minute) was then calculated for central (C3, C4) frontal (F3, F4), and occipital (O1, O2) EEG channels for each participant. Several studies have used this method to probe the role of spindles in sleep dependent memory consolidation.[20,40–42]

Data Analysis

Picture Locations

For all participants, we created a picture-location error score for the pre-sleep and post-sleep tests by calculating the distance (cm) between each recalled picture location and the correct picture location (i.e., the location encoded in the passive viewing phase). Because errors in picture-recall accuracy typically increase over time,[14,15] the picture-location error score for the pre-sleep test was then subtracted from that of the post-sleep test to produce a memory decay index (MDI) for each trial. Thus, a benefit of TMR for consolidation was expected to manifest in a lower mean MDI for the picture locations that were cued by their associated sounds in sleep (i.e., "replayed picture locations") than for the noncued picture locations (i.e., "nonreplayed picture locations"). To quantify the memory benefits of TMR within a single measure, we calculated a "TMR Effect" by subtracting the mean MDI for replayed picture locations from the mean MDI for nonreplayed picture locations, such that a positive TMR Effect corresponded to less memory decay for replayed items (versus nonreplayed items).

Picture-Word Pairs

Memory for the picture-word pairs was assessed by the number of correct words retrieved in the cued recall tests. Because of the correct/incorrect word feedback provided in the pre-sleep tests, cued recall performance was expected to improve over sleep.[34–37] A memory benefit of TMR could therefore be detected by greater recall improvement for words associated with replayed picture locations than for words associated with nonreplayed picture locations.

RESULTS

Sleep and Alertness Ratings

Participant estimations of hours slept during the night preceding the study (mean ± SD, 7.72 ± 0.73) did not significantly differ from their estimations of hours slept in a typical night (mean ± SD, 7.99 ± 0.88, $t(29) = 1.41$; P = 0.17), suggesting that participants' pre-study sleep had not deviated from their usual practices.

Subjective levels of alertness, as measured with the Stanford Sleepiness Scale,[33] were the same in the pre-sleep (mean ± SD, 2.73 ± 0.74) and post-sleep sessions (mean ± SD, 2.63 ± 0.72, ($t(29) = 0.53$; P = 0.60). Moreover, there was no relationship between nap time spent in SWS and post-sleep response times for all items in both the picture-location test ($r = 0.003$; P = 0.99)

Table 1—Picture-location recall: high and low performers.

	All Participants			Low-Acc Performers			High-Acc Performers		
	Combined	TMR	No TMR	Combined	TMR	No TMR	Combined	TMR	No TMR
Pre-sleep location error score (cm)	2.86 ± 0.15	2.91 ± 0.16	2.81 ± 0.15	3.54 ± 0.16	3.59 ± 0.17	3.49 ± 0.17	2.19 ± 0.07	2.24 ± 0.09	2.14 ± 0.07
Post-sleep location error score (cm)	3.27 ± 0.19	3.19 ± 0.19	3.35 ± 0.22	4.04 ± 0.23	3.85 ± 0.26	4.22 ± 0.25	2.50 ± 0.13	2.52 ± 0.15	2.49 ± 0.15
Memory decay index (cm)	0.41 ± 0.10	0.27 ± 0.11	0.54 ± 0.12	0.50 ± 0.15	0.27 ± 0.19	0.74 ± 0.18	0.32 ± 0.12	0.28 ± 0.14	0.35 ± 0.15

Data are shown as mean ± standard error of the mean. Picture-location error scores (recalled location – correct location) and memory decay indices (post-sleep picture-location error score – pre-sleep picture-location error score) for all participants and participants allocated to groups of low accuracy (Low-Acc) performers and high accuracy (High-Acc) performers in the pre-sleep test. TMR, targeted memory reactivation. 1 cm = 31.25 screen pixels.

Table 2—Picture-location recall: high- and low-accuracy items.

	Low-Acc Items			High-Acc Items		
	Combined	TMR	No TMR	Combined	TMR	No TMR
Number of items	23.50 ± 0.09	11.83 ± 0.12	11.67 ± 0.14	23.90 ± 0.09	11.97 ± 0.12	11.93 ± 0.12
Pre-sleep location error score (cm)	3.73 ± 0.21	3.75 ± 0.22	3.71 ± 0.20	1.01 ± 0.04	1.01 ± 0.04	1.01 ± 0.04
Post-sleep location error score (cm)	4.12 ± 0.26	3.96 ± 0.28	4.29 ± 0.26	1.87 ± 0.13	1.91 ± 0.14	1.82 ± 0.16
Memory decay index (cm)	0.40 ± 0.11	0.21 ± 0.13	0.58 ± 0.14	0.85 ± 0.11	0.89 ± 0.12	0.81 ± 0.15

Data are shown as mean ± standard error of the mean. Picture-location error scores (recalled location – correct location) and memory decay indices (post-sleep picture-location error score – pre-sleep picture-location error score) for items allocated to categories of low pre-sleep accuracy (Low-Acc) and high pre-sleep accuracy (High-Acc). Outlier trials for which the pre-sleep picture-location error score was 2 SDs higher than the participant mean were excluded. In the High-Acc category, pre-sleep location error scores for the TMR and No TMR conditions were identical to two decimal places. TMR, targeted memory reactivation. 1 cm = 31.25 screen pixels.

and picture-word test ($r = -0.03$; P = 0.89), indicating that behavioral changes were unlikely to have occurred as a result of participant differences in homeostatic sleep pressure.[40,43–45]

Targeted Memory Reactivation

Picture Locations

A 2 (session: pre-sleep / post-sleep) × 2 (TMR: on / off) repeated-measures analysis of variance (ANOVA) conducted on picture-location error scores (distance between recalled location and correct location) revealed a main effect of session ($F(1,29) = 18.53$; P < 0.0001), indicating that location accuracy was significantly better in the pre-sleep test than the post-sleep test. Considering both pre- and post-sleep results, there was no main effect of TMR condition ($F(1,29) = 0.14$; P < 0.71). Of most relevance to our predictions, a marginal session*TMR interaction ($F(1,29) = 4.00$; P = 0.055) indicated that MDIs (post-sleep location error score – pre-sleep location error score) were lower for replayed picture locations than nonreplayed picture locations (see Table 1). The TMR effect (MDI for nonreplayed picture locations – MDI for replayed picture locations) was not significantly correlated with the number of sound-set replays that took place during sleep ($r = 0.23$; P = 0.22).

To examine how memory accuracy prior to sleep influenced the effectiveness of TMR, we carried out a median split on the 50 picture-location error scores from the pre-sleep test for each participant, which resulted in two categories of high pre-sleep location accuracy (High-Acc) and low pre-sleep location accuracy (Low-Acc, see Table 2). So that any observable benefit of TMR for Low-Acc items was not driven by individual cases of extremely poor accuracy, outlier trials for which the pre-sleep picture-location error score was 2 SDs higher than the participant mean were excluded beforehand. Across the 1,500 trials examined over all 30 participants, a total of 78 trials (5.2%) were excluded (mean ± SEM number of trials excluded per participant = 2.60 ± 0.16).

There were comparable numbers of replayed and nonreplayed sounds in both the Low-Acc category ($t(29) = 0.69$; P = 0.49) and High-Acc category ($t(29) = 0.15$; P = 0.88), and pre-sleep location error scores for subsequently replayed and nonreplayed picture locations were equivalent in both categories (Low-Acc: $t(29) = 0.58$; P = 0.57, High-Acc: $t(29) = 0.03$; P = 0.98). Importantly, a 2 (accuracy: high / low) × 2 (TMR: on / off) repeated-measures ANOVA conducted on MDIs revealed a significant accuracy*TMR interaction ($F(1,29) = 6.12$; P = 0.019), indicating that the benefits of TMR for consolidation were contingent on the accuracy with which memories were recalled prior to sleep (see Figure 2). Subsequent paired samples *t*-tests revealed a significant TMR effect (nonreplayed MDI – replayed MDI) in the Low-Acc category ($t(29) = 2.19$; P = 0.037) but not in the High-Acc category ($t(29) = 0.54$; P = 0.60). Across replayed and nonreplayed items, MDIs were larger in the High-Acc category than in the Low-Acc category (accuracy main effect: $F(1,29) = 14.20$; P = 0.001), indicating that high accuracy memories were more prone to general decay than low accuracy memories. There was no main effect of TMR ($F(1,29) = 1.12$; P = 0.30). For completeness, we conducted the same repeated-measures ANOVA as previously discussed on the original data (i.e. including outlier trials) and this also revealed a significant accuracy*TMR interaction ($F(1,29) = 8.21$; P = 0.008).

In keeping with prior work,[13] we also carried out a median split on mean picture-location error scores in the pre-sleep test to create two equally sized groups of "High-Acc performers" and "Low-Acc performers" (see Table 1). A 2 (group: High-Acc performers / Low-Acc performers) × 2 (TMR: on / off) mixed ANOVA conducted on MDIs revealed a main effect of TMR ($F(1,28) = 4.22$; $P = 0.049$), demonstrating that replayed picture locations were better recalled than nonreplayed picture locations. Although the TMR effect was numerically higher in Low-Acc performers relative to High-Acc performers, there was no significant interaction between factors $F(1,28) = 2.46$; $P = 0.13$. There was no main effect of group ($F(1,28) = 0.97$; $P = 0.33$).

Picture-Word Pairs

A 2 (session: pre-sleep / post-sleep) × 2 (TMR: on / off) repeated-measures ANOVA conducted on cued recall scores revealed a main effect of session ($F(1,29) = 61.46$; $P < 0.0001$), indicating that the correct / incorrect word feedback in the final pre-sleep test had improved cued recall performance over sleep. However, there was no significant interaction between session and TMR ($F(1,29) = 0.024$; $P = 0.88$), demonstrating that words associated with replayed picture locations were not better remembered than words associated with non-replayed picture locations. There was also no main effect of TMR ($F(1,29) = 0.00$; $P = 1.0$).

A median split was conducted on mean cued recall scores in the pre-sleep test to create two equal groups of "word high performers" and "word low performers" (see Table 3). Cued recall improvement scores (post-sleep cued recall score – pre-sleep cued recall score) were applied to a 2 (group: word high performers / word low performers) × 2 (TMR: on / off) mixed ANOVA. This revealed no main effect of TMR ($F(1,28) = 0.02$; $P = 0.88$) and no interaction between factors ($F(1,28) = 0.21$; $P = 0.65$), indicating no general or performance-dependent benefit of TMR for memories that were indirectly linked to the acoustic cues. A main effect of group showed that the cued recall performance improvement was greater for word low performers than word high performers ($F(1,28) = 17.37$; $P < 0.0001$).

Sleep Stages

Sleep stage data are available in Table 4. Because of the time of day at which sleep took place, REM sleep did not emerge in 21 of the 30 study participants (70%) and was excluded from our analyses. SWS predicted the TMR effect for outlier-corrected Low-Acc picture locations ($r = 0.38$; $P = 0.036$) but not High-Acc picture locations ($r = 0.10$; $P = 0.62$, Hotelling $t(27) = 1.44$; $P = 0.16$). As shown in Figure 3, SWS was correlated with the MDI for nonreplayed Low-Acc picture locations ($r = 0.41$; $P = 0.024$) but not the MDI for replayed Low-Acc picture locations ($r = -0.06$; $P = 0.76$, Hotelling $t(27) = 2.15$; $P = 0.041$).

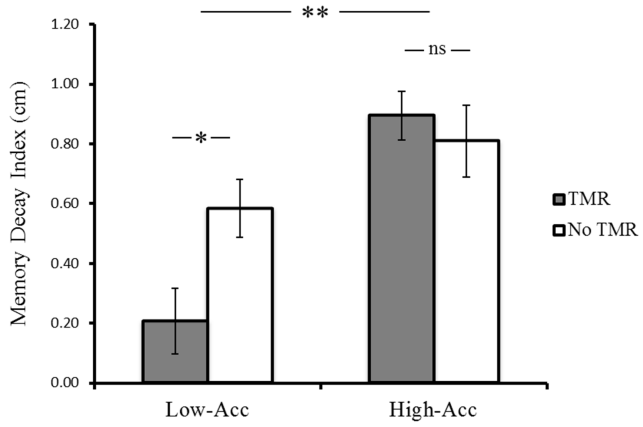

Figure 2—The memory decay index (post-sleep picture-location error score – pre-sleep picture-location error score) was significantly lower for replayed picture locations than nonreplayed picture locations in the low pre-sleep accuracy (Low-Acc) category but not in the high pre-sleep accuracy (High-Acc) category (outlier-corrected data). Error bars represent within-subject standard error of the mean (*paired samples *t*-test; $P < 0.05$, **analysis of variance interaction; $P < 0.05$). ns, not significant; TMR, targeted memory reactivation.

Table 3—Picture-word recall.

	All Participants			Low Performers			High Performers		
	Combined	TMR	No TMR	Combined	TMR	No TMR	Combined	TMR	No TMR
Pre-sleep %	75.40 ± 2.14	75.47 ± 2.14	75.33 ± 2.16	65.20 ± 1.22	65.60 ± 1.34	64.80 ± 1.18	85.60 ± 1.60	85.33 ± 1.82	85.87 ± 1.45
Post-sleep %	86.07 ± 1.54	86.00 ± 1.77	86.13 ± 1.68	80.40 ± 1.85	80.27 ± 2.39	80.53 ± 2.02	91.73 ± 1.32	91.73 ± 1.58	91.73 ± 1.77
Improvement %	10.67 ± 1.36	10.53 ± 1.52	10.80 ± 1.71	15.20 ± 1.82	14.67 ± 2.13	15.73 ± 2.29	6.13 ± 1.19	6.40 ± 1.60	5.87 ± 1.83

Data are shown as mean ± standard error of the mean. Picture-word cued recall scores and improvement scores (post-sleep cued recall score – pre-sleep cued recall score) for all participants and participants allocated to low- and high-performing groups in the pre-sleep test. TMR, targeted memory reactivation.

Table 4—Sleep stages.

Stage I	Stage II	SWS	REM	TST (min)	WASO (min)
19.71 ± 1.71	38.23 ± 2.38	38.94 ± 3.34	3.13 ± 1.17	72.88 ± 2.99	16.38 ± 2.30

Data are shown as mean ± standard error of the mean. Percentage of total sleep time (TST) spent in each stage of sleep. REM, rapid eye movement; SWS, slow wave sleep; WASO, wake after sleep onset. Only 9 of the 30 participants obtained REM sleep during their nap.

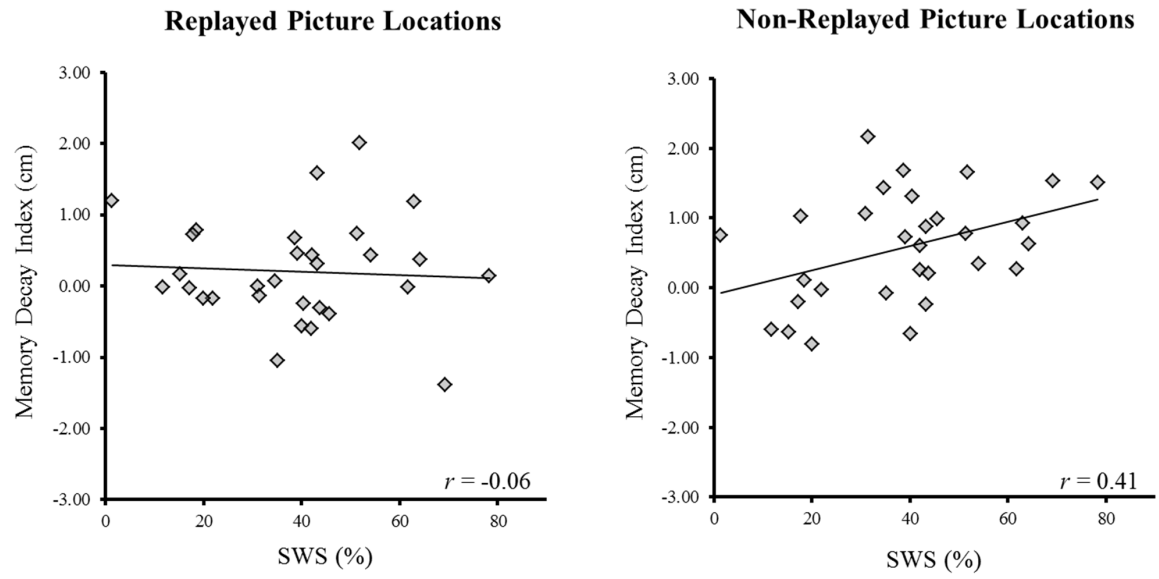

Figure 3—In the low pre-sleep accuracy category, the percentage of total sleep time spent in slow wave sleep (SWS) predicted the memory decay index (post-sleep picture-location error score – pre-sleep picture-location error score) for nonreplayed picture locations but not replayed picture locations. The difference between these correlations was statistically significant ($t(27) = 2.15$; P = 0.041).

Table 5—Spindle density.

	All	F3	F4	C3	C4	O1	O2
Fast spindle density	0.78 ± 0.06	1.11 ± 0.09	1.04 ± 0.08	0.96 ± 0.07	0.92 ± 0.08	0.32 ± 0.05	0.30 ± 0.05
Slow spindle density	0.67 ± 0.05	1.12 ± 0.09	1.00 ± 0.08	0.71 ± 0.07	0.72 ± 0.07	0.22 ± 0.03	0.21 ± 0.03

Data are shown as mean ± standard error of the mean. Sleep spindle density (counts per minute) in the fast (13.5–15 Hz) and slow (12–13.5 Hz) frequency bands for each electroencephalography channel during stage II sleep and slow wave sleep.

TMR effects for Low-Acc items and High-Acc items were not correlated with time spent in any other sleep stage or total sleep time (all P > 0.1).

Sleep Spindles

Neither fast (13.5–15 Hz) nor slow (12–13.5 Hz) sleep spindle density, as averaged across the six EEG channels, predicted the TMR effect for Low-Acc picture locations (fast spindle density: $r = -0.22$; P = 0.25, slow spindle density: −0.34; P = 0.07) or High-Acc picture locations (fast spindle density: $r = 0.32$; P = 0.09, slow spindle density: $r = 0.25$; P = 0.19). Spindle density data are available in Table 5.

Sound Discrimination

All participants professed to having no knowledge of sound replay taking place during sleep and were unable to discriminate between the sounds that were replayed and those that were not ($t(29) = 0.58$; P = 0.57).

DISCUSSION

We investigated how the benefits of TMR for consolidation are influenced by the accuracy with which newly learned memories are recalled prior to sleep and the presence or absence of direct cue-memory associations. Our data showed that picture-location memories decayed to a lesser extent over sleep when the sounds directly associated with those memories at encoding were (versus were not) replayed in SWS, suggesting an overall modulatory effect of TMR on sleep dependent consolidation. Further analyses revealed a benefit of TMR for picture locations recalled with a low degree of accuracy prior to sleep, but not picture locations recalled with a high degree of accuracy. This selective benefit of TMR for low accuracy picture-location memories was also predicted by time spent in SWS; a relationship driven by a correlation between SWS and the memory decay for nonreplayed picture locations.

For the picture-word memories, by contrast, we observed no difference in cued recall performance for words associated with replayed picture locations relative to words associated with nonreplayed picture locations, irrespective of performance in the pre-sleep test, suggesting that memories with indirect links to the acoustic cues receive no benefit of TMR. We discuss each of our key findings in turn in the next paragraphs.

Memory Accuracy prior to Sleep

Building on prior work,[14,15] our findings demonstrate that the extent to which picture-location memories benefit from TMR is contingent on the accuracy with which those memories are recalled prior to sleep. Having assigned the picture locations

to categories of high or low pre-sleep accuracy for each participant, our within-subjects analysis showed that replayed picture locations were better recalled than nonreplayed picture locations in the low accuracy category but not in the high accuracy category. Furthermore, a separate group analysis based on mean pre-sleep performance revealed that the memory advantage for replayed relative to non-replayed picture locations was numerically higher in the low-performing group than in the high-performing group, though this difference was not statistically significant. Taken together, these findings suggest that memories with weaker representations are most responsive to TMR.

The influence of pre-sleep performance on the success of TMR was also investigated in a recent study by Creery et al.[13] In keeping with our findings, a within-subjects analysis revealed the greatest and only significant benefit of TMR for picture locations assigned to a category of low pre-sleep accuracy. In contrast to our data, however, a separate comparison of high and low performers in the pre-sleep test revealed a benefit of TMR in only the high-performing group, leading the authors to conclude that TMR supports consolidation provided that recall prior to sleep is neither too strong nor too weak. Although we observed no significant interaction between pre-sleep performance group and TMR, it is unclear why our analysis yielded such different results to those of Creery et al., particularly as they were obtained with the same picture-location task. A potential source of this discrepancy lies in the execution of the experimental paradigm. In the current study, the pre-sleep test began immediately after training (active learning), whereas Creery et al. placed a ~45 min delay between training and test, during which memory decay may have occurred. The difference in pre-sleep picture-location error scores between the two studies was negligible (mean ± SEM, current study: 2.86 ± 0.15 cm, Creery et al.: 3.10 ± 0.16 cm, $t(48) = 1.04$; $P = 0.30$), but given that the participants of Creery et al. were at this level of performance after a longer retention interval it is possible that these individuals were overall better learners than the participants of the current study. Such a difference in baseline learning ability might explain why the two studies differ in terms of the influences of TMR on groups of high and low performers. Nevertheless, as we did not include a pre-sleep test ~45 min after training, we can only speculate about the causes of these divergent findings. Thus, although both the current study and the study of Creery et al. provide evidence for a prioritization of weaker memories by TMR, further research is necessary to examine how overall learning performance interacts with the effectiveness of TMR for consolidation.

A preferential benefit of TMR for low-accuracy memories corroborates the view that memory reactivations in sleep underpin the stabilization and long-term storage of initially weak and labile memory traces and, hence, provide little support to memories that already possess strong and enduring representations.[3,46] An earlier study, for example, found a memory benefit of sleep for word pairs learned to a criterion of 60% correct, but no effect of sleep for word pairs learned to a criterion of 90% correct.[26] TMR may therefore enhance the typical pattern of consolidation that takes place in the sleeping brain and preferentially facilitate the stabilisation of weaker representations. Nevertheless, it is important to note that memories recalled with a low degree of accuracy do not necessarily possess weak representations, and thus the discriminatory effects of TMR cannot be attributed to memory strength alone. This view is also difficult to reconcile with recent work indicating that highly salient memories, which presumably carry stronger representations than nonsalient memories, have the greatest access to sleep dependent consolidation.[47] However, the benefits of sleep for highly salient memories are thought to arise from a form of neural "tagging" at encoding.[1,5] From this perspective, and in keeping with prior work,[20] it is possible that TMR induces a retrospective tagging of weakly encoded memories and, thereby, prompts a targeted consolidation process in subsequent SWS.

A Role for SWS?

Time spent in SWS predicted the memory benefit of TMR for picture locations recalled with a low degree of accuracy but not picture locations recalled with a high degree of accuracy, although the difference between these correlations did not reach statistical significance. Nonetheless, this finding is in keeping with earlier work linking SWS to the recall advantage for reactivated (versus nonreactivated) memories following TMR,[28] as well as the view that TMR initiates an augmented consolidation process during subsequent SWS.[20] Building on these studies, our findings may provide preliminary evidence that the benefits of SWS for consolidation after TMR are determined by the accuracy with which new information is recalled prior to sleep. Furthermore, because SWS predicted the memory decay of non-replayed low accuracy memories, but not replayed low accuracy memories, it is also possible that SWS inhibits (i.e., suppresses) the systems-level consolidation of nonreactivated low- accuracy representations and thereby supports the strengthening of their reactivated counterparts indirectly. Indeed, previous work has suggested that newly learned memories can be tagged for both selective forgetting and retention during sleep,[48] and other research has indicated that SWS can have both enhancing and inhibitory influences on consolidation.[49,50] Therefore, TMR may have taken on the enhancement role normally fulfilled by SWS and facilitated consolidation through hippocampal replay, leaving just the inhibition of nonreactivated memories to be accomplished during subsequent SWS.

The relationship between SWS and nonreplayed low accuracy picture-location memories can also be linked to the synaptic homeostasis hypothesis (SHY).[51–53] According to SHY, SWS promotes a global and proportional downscaling of synapses potentiated throughout the preceding day as a result of learning, and thus improves the signal-to-noise ratio within cortical memory circuitry. Highly potentiated neuronal connections therefore retain their synaptic strength relative to weakly potentiated connections, which may even be downscaled below an active threshold and rendered silent. From this perspective, SWS and synaptic downscaling may normally have a harmful effect on all low-accuracy memories that are underpinned by potentially weak synaptic connections. TMR during SWS, however, may counteract the detrimental influences of synaptic downscaling for the reactivated low-accuracy

memory representations by selectively boosting the strength of their neuronal connections. Consequently, only nonreactivated low accuracy memories would be harmed by downscaling and the extent of this impairment would be predicted by SWS. These are nevertheless highly speculative conclusions, which should be substantiated with further research.

We observed no relationship between spindle density and the memory benefits of TMR. Whereas this finding deviates from studies that have linked spindles to successful acoustic memory cuing in sleep,[20,21,28] others that employed the same picture-location task as the current study yielded inconsistent findings, with the majority showing no influence of sleep spindles.[13–15,22] Moreover, the study that linked the visuospatial memory benefits of TMR to sleep spindles was focused on the parietal cortex,[13] an area from which EEG recordings were not obtained in the current study. The role of spindles in visuospatial memory consolidation following TMR may therefore be difficult to detect with the current experimental paradigm.

An important point to note in relation to the aforementioned findings is that this study did not include a comparison of TMR across wakefulness, thereby making it unclear as to whether the observed effects of TMR were sleep-specific. However, earlier work has indicated that acoustic or olfactory cues delivered in wakefulness have either no effect on consolidation[15,18] or a qualitatively different effect on consolidation to the same cues delivered in sleep.[14,17] Furthermore, findings from animal studies have indicated that although memory reactivations occur in both sleep and wakefulness,[10,54–56] they are of a qualitatively different nature and potentially reflect distinct consolidation processes.[6] Thus, although the effects of wakeful TMR on consolidation, if any, may also be modulated by the accuracy with which memories are recalled prior to sleep, it is entirely possible that such effects would be different to those observed in the current study.

Cue-Memory Associations

Our data showed no benefit of TMR for picture-word memories that were indirectly linked to the acoustic cues. This was the case for both the overall analysis that encompassed all participants and the comparative group analysis of high and low performers in the pre-sleep test. These findings therefore indicate that the success of TMR may be partly dependent on direct cue-memory associations, which in the case of this study were those ascribed to the picture-location memories. Because prior research has suggested that sleep supports relational memory,[25] a consolidation benefit of TMR via indirect cue-memory associations might have also been expected. However, it is possible that a rich period of endogenous sleep was required to first generalize the acoustic cues to the nondirectly associated memories before a memory benefit of TMR could emerge. As such, the short period of sleep that preceded TMR in this study may have been insufficient for this process to complete, resulting in a null effect of TMR in cued recall. This view is substantiated by other work linking relational memory processing specifically to REM sleep,[57] because most participants in the current study failed to achieve REM sleep during their nap.

The active systems model places particular emphasis on the importance of hippocampal memory reactivations for consolidation during sleep.[4,6] Recent work on TMR has provided compelling support for this view by demonstrating that the memory benefits of acoustic cuing in sleep are contingent on the functional integrity of the hippocampus.[21] A null effect of TMR for the picture-word pairs in the current study provides some extension to this work by suggesting that hippocampal replay, during the first cycle of sleep at least, may selectively strengthen memories linked to the reactivation cues directly. On account of the importance of the hippocampus and wider MTL region for relational memory processing,[58] it is possible that, across longer periods of sleep, the memory gains resulting from hippocampal replay may extend to memories that are indirectly linked to the reactivation cues.

It is nevertheless important to exercise caution with this result for several reasons. Whereas the picture-location task adopted in this study provides a highly precise measure of memory accuracy, it is possible that our picture-word task (i.e., with a binary correct / incorrect memory measurement) was less sensitive to any effects of TMR. Indeed, there is also no clear evidence that picture-word pairs can be strengthened via TMR with even direct cue-memory associations. Although Fuentemilla et al.,[21] for example, observed a benefit of TMR for paired associate-like representations (sound-word associations), their task also required participants to encode a screen location for each word, suggesting that the spatial memory component of their task might have enhanced the responsiveness of the new information to TMR. Indeed, other recent studies have also shown improvements in non-spatial language-based tasks after TMR, but these used the learned verbal materials as reactivation cues in sleep, rather than associated sounds.[59–62]

It is also possible that TMR was ineffective in strengthening paired-associate memory because the acoustic cues were not semantically related to the words of each pair. The majority of prior studies have demonstrated a benefit of TMR for consolidation with sounds that have a clear semantic link to the learned materials (e.g. a picture of a cat and a "meow" sound),[13-15,20] as was the case in the picture-location task of the current study. Although the study of Fuentemilla et al.[21] revealed a memory benefit of replaying sounds in sleep that were not semantically related to their associated words, the reactivation cues themselves formed the acoustic portion of each sound-word pair and were therefore a critical component of the learned information. TMR with indirect cue-memory associations may thus be more effective for consolidation in sleep when there is a clear semantic link between the acoustic cues and the newly learned memories.

Furthermore, it may be that other procedural factors, such as the fixed order of the experimental tasks or the correct / incorrect word feedback at training, prevented a benefit of TMR from emerging in picture-word recall. Future research that accounts for such factors is therefore crucial for properly determining whether TMR with indirect cue-memory associations has any effect on consolidation in sleep.

Finally, if low-accuracy picture-location memories are more responsive to TMR because they have weaker representations, then one might expect TMR to also strengthen indirect cue-memory associations, which are presumably weak by their nature. Collectively, however, these potentially conflicting

findings may provide further insight to the characteristics of newly formed memories that are highly responsive to TMR. Rather than indiscriminately strengthening all weak memory components (inclusive of indirect cue-memory associations), TMR may provide the greatest support to consolidation when there is a weakly recalled link between two components of a single memory (i.e., a picture and a location) that is strongly associated with a reactivation cue. Accordingly, the benefits of TMR for low accuracy picture-location memories may be critically dependent on the presence of direct cue-memory associations.

CONCLUSIONS

Our data extend previous research by demonstrating that TMR delivered in SWS provides the greatest benefit to memories recalled with a low degree of accuracy prior to sleep. Moreover, our findings suggest that the seemingly preferential benefits of TMR for low-accuracy memories are mediated by SWS, which may support reactivated memories by inhibiting the consolidation of their nonreactivated counterparts. Finally, our data also suggest that the benefits of TMR for consolidation may be contingent on the presence of direct cue-memory associations.

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