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RESEARCH ARTICLE

Improving memory via automated targeted memory reactivation during sleep

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Summary

A widely accepted view in memory research is that previously acquired information can be reactivated during sleep, leading to persistent memory storage. Targeted memory reactivation (TMR) was developed as a technique whereby specific memories can be reactivated during sleep using a sensory stimulus linked to prior learning. As a research tool, TMR can improve memory, raising the possibility that it may be useful for cognitive enhancement and clinical therapy. A major challenge for the expanded use of TMR is that a skilled operator must manually control stimulation, which is impractical in many settings. To address this limitation, we developed the SleepStim system for automated TMR in the home. SleepStim includes a smartwatch to collect movement and heart-rate data, plus a smartphone to emit auditory cues. A machine-learning model identifies periods of deep sleep and triggers TMR sounds within these periods. We tested whether this system could replicate the spatial-memory benefit of in-laboratory TMR. Participants learned locations of objects on a grid, and then half of the object locations were reactivated during sleep over 3 nights. Recall was tested each morning. In an experiment with 61 participants, the TMR effect was not significant but varied systematically with stimulus intensity; low-intensity but not high-intensity stimuli produced memory benefits. In a second experiment with 24 participants, we limited stimulus intensity and found that TMR reliably improved spatial memory, consistent with effects observed in laboratory studies. We conclude that SleepStim can effectively accomplish automated TMR, and that avoiding sleep disruption is critical for TMR benefits.

KEYWORDS
memory consolidation, memory replay, sleep, sleep disruption, wearable technology

INTRODUCTION

Sleep has long been recognised as important for memory (e.g., Patrick & Gilbert, 1896), but much remains to be learned about why. A prevalent view at the present time is that reactivation of stored information during sleep helps stabilise memories, preventing forgetting of important information (Born & Wilhelm, 2012; Marr, 1971; Paller, 1997; Paller et al., 2020).

Studies using targeted memory reactivation (TMR) have provided evidence for this hypothesis by demonstrating that selectively reactivating memories during sleep can strengthen them (Oudiette & Paller, 2013). In TMR experiments, learning is associated with a sensory cue, which is subsequently presented during sleep without awaking the sleeper. Cue presentation can lead to reactivation of memory content in the cortex and hippocampus (Bendor & Wilson, 2012; Cairney et al., 2018; Wang et al., 2019). After sleep, reactivated memories are

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typically remembered better than those not reactivated, demonstrating that memory reactivation during sleep can strengthen memory, a finding that has been confirmed by meta-analysis (Hu et al., 2020).

Experiments with TMR have shown that it is a useful tool for investigating questions in memory research and potentially as an intervention for cognitive enhancement. For example, TMR can improve retention of information learned in a classroom setting (Gao et al., 2020) and facilitate learning of motor skills (Cheng et al., 2021; Johnson et al., 2019). Researchers have therefore proposed that TMR may be useful to enhance memory and to augment therapies that depend on learning, e.g., rehabilitation (Oudiette & Paller, 2013; Paller, 2017).

A major barrier to expanding use of TMR is that the technique requires experimenters to control presentation of cues while monitoring sleep using polysomnography (PSG). In this way, cues can be presented in a particular sleep stage without arousing the participant from sleep. A specialised sleep facility and extensive training of operators is required for this online sleep scoring, and participants must sleep in an environment that differs in many ways from their typical sleeping environment at home.

These requirements impose substantial limitations on TMR experiments. For example, very few studies have examined the effects of multiple TMR sessions, owing largely to logistical difficulties. Standard TMR requirements also make it impractical to study or use TMR in clinical therapy across multiple sessions. To surmount these limitations, new ways to perform TMR in participants' own homes are needed, ideally using an automated system that does not require direct control by an operator.

Previous research on TMR outside of the sleep laboratory

Previous research on home-TMR can be divided into two categories. With brain-state-independent approaches (Antony et al., 2022), TMR cues are automatically presented during sleep irrespective of sleep stage. In brain-state-dependent approaches, there is an attempt to present TMR cues in a specific sleep stage.

Brain-state independent TMR has shown mixed results in improving cognition and memory. Ritter et al. (2012) found that memory reactivation during sleep could enhance creative problem solving; the researchers reactivated a problem-solving task using a plug-in scent diffuser during overnight sleep. While they slept, participants received either an odour linked to the task, an irrelevant odour, or no odour, and those who received task-linked odours produced solutions that blinded raters judged as more creative. Similarly, Neumann et al. (2020) found that TMR with an olfactory cue (incense sticks placed near the head while sleeping) could improve vocabulary learning in children. Other brain-state independent TMR experiments, in contrast, did not find benefits consistent with the TMR literature. Donohue and Spencer (2011) found that TMR using a continuous ocean sound played while participants slept overnight did not improve memory for word pairs. Göldi and Rasch (2019) found no effect of TMR when foreign vocabulary was cued 30 min after sleep onset. However, in a further analysis the authors showed that TMR benefitted memory for participants who reported that their sleep was undisturbed, but not those who reported that sound cues disturbed their sleep.

Our recent experiments using PSG recordings in the laboratory environment substantiated the notion that Göldi and Rasch (2019) put forward – that TMR does not improve memory when sleep is disrupted by sounds. One study showed that a TMR benefit for learning face-name associations was reduced when TMR sounds disrupted sleep (Whitmore et al., 2022). Furthermore, deliberately disrupting sleep with loud sound cues reverses the TMR effect on spatial recall, selectively weakening reactivated memories (Whitmore & Paller, 2022). Therefore, we suggest that brain-state independent TMR may tend to be ineffective because the intensity and timing of cues cannot be flexibly adjusted to avoid disrupting sleep.

Accordingly, brain-state dependent home TMR controlled using a sleep sensor may be superior to brain-state independent TMR. In two prior experiments with home TMR, we used a modified Zeo system (Shambroom et al., 2012) with electrolyte-filled electrodes for forehead electroencephalography (EEG) recordings used to control sound presentations. One study showed an impact of TMR on feelings of ownership and proprioceptive drift in the rubber-hand illusion (Honma et al., 2016). The other showed effects on creative problem solving (Sanders et al., 2019).

Designing a home TMR system

Based on previous research and pilot testing, we identified key needs for a home TMR system. These included the ability to target specific sleep stages, robustness to signal problems (such as poor contact quality), and minimal reliance on proprietary or 'black-box' technology. The system must also be comfortable, avoid disturbing sleep, and be easy for participants to use.

As no complete system currently exists meeting these requirements, we developed a new open-loop, brain-state dependent TMR system that we call 'SleepStim'. This system works with consumer devices, specifically an Android phone and a Fitbit smartwatch. Previous research has shown that sleep stages can be decoded from heart rate and wrist movement (Beattie et al., 2017; de Zambotti et al., 2018; Faust et al., 2019); although these algorithms are less accurate than traditional sleep scoring they can still provide useful information on sleep (Haghayegh et al., 2019). We developed a custom algorithm to identify periods of N3 sleep and trigger TMR cueing during these periods (without the need to discriminate all sleep stages). We then tested whether TMR with SleepStim could improve memory for object-location associations as observed in previous TMR studies (e.g., Rudoy et al., 2009).

EXPERIMENT 1 METHODS

Figure 1 shows a diagram of the 5-day procedure. On the first day, we provided participants with a Fitbit Versa and an Android smartphone. To allow us to correlate sleep-physiology features with behavioural results, a Dreem 2 headband (Arnal et al., 2020) was also provided. On

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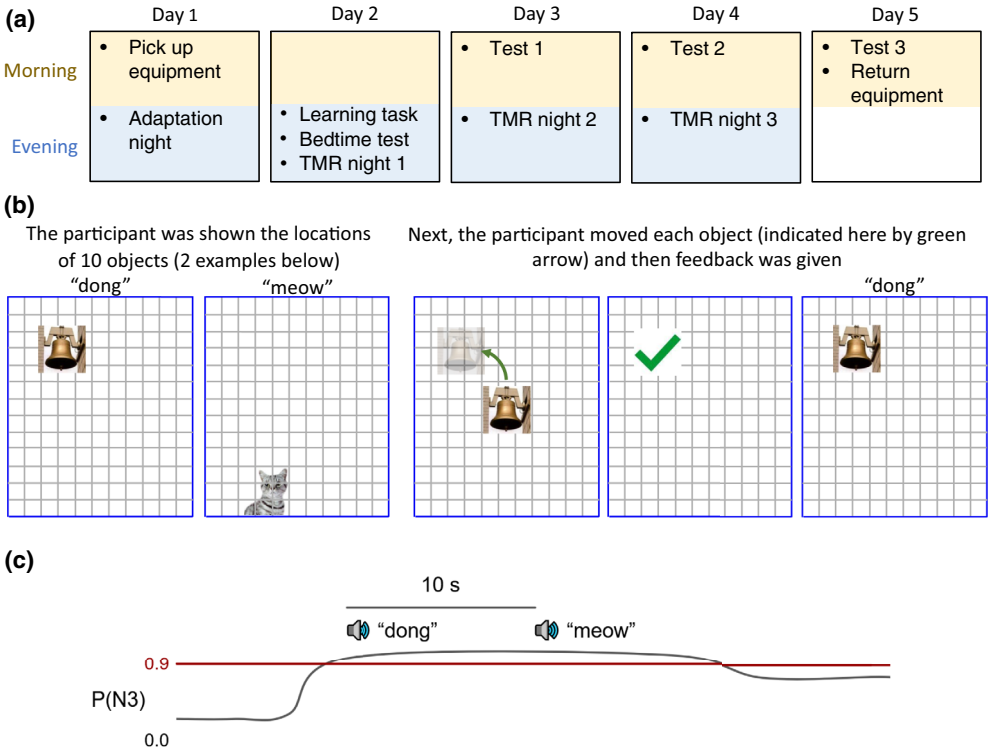

FIGURE 1 (a) Sequence of events in the study. On day 2 all tasks were completed in the evening. (b) the learning phase included five blocks with 10 objects each. Each block included presentation of objects (left) and trials of location recall with the drop-out method (right). The sound of each object was played whenever the object appeared on the screen in its target location. The memory test used the same procedure for location recall except that participants were not given feedback or shown the correct location of the objects, and the sounds were not played. (c) Diagram of the cue-control algorithm. When average probability of N3 passes the threshold (0.9), cues are played every 10 s. Cueing stops when *p* (N3) drops below this threshold or an arousal is detected.

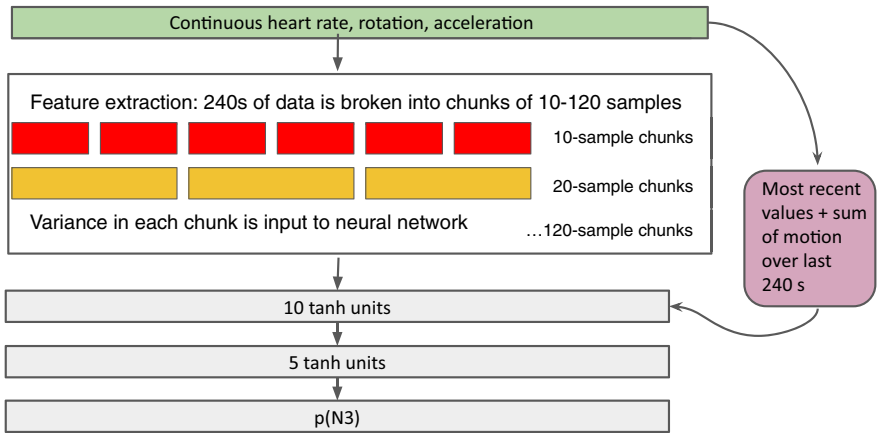

FIGURE 2 Schematic of the feature-extraction system and neural network. Variance was calculated using the standard deviation of each chunk.

the second day, participants learned arbitrary screen locations for 50 objects shown on a grid on the smartphone. Each object appeared with a distinct sound naturally associated with the object (mean [SD] duration 554 [181] ms). On the second, third, and fourth night, the SleepStim system presented sound cues for half of the objects during sleep. Memory was tested in the morning of the third, fourth, and fifth day. We predicted that participants would recall locations more accurately for objects reactivated during sleep compared to those not reactivated, replicating the typical effect of TMR on spatial memory.

SleepStim system

The SleepStim system was designed to present TMR cues in N3 sleep, detected using a Fitbit worn by participants. A custom application running on the Fitbit acquired data once per second. Data consisted of heart rate in beats per minute, acceleration on *x*-, *y*-, and *z*-axis, and rotation on these axes from the accelerometer and gyro, respectively. Data were transmitted via Bluetooth to the paired phone. The first step of processing on the phone was feature extraction, as schematised in Figure 2. Briefly, the phone computed a time-frequency representation of the last 240 s of accelerometer, gyro, and heart-rate data. The result was a time-frequency matrix, quantifying variability as a function of both time (number of prior seconds) and frequency. This transformation is similar to that used in other sleep-staging algorithms (Beattie et al., 2017) and is useful because it allows for characterisation of various sleep phenomena (e.g., high- versus low-frequency heart rate variability). Because time-frequency variability was highly correlated on all axes, only the *z*-axis of the accelerometer and gyro signals was used in computing the time-frequency representation.

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Following feature extraction, the time-frequency features along with current values from all sensors and total motion integrated over the last 240 s were input to an artificial neural network classifier trained to predict the probability of N3 sleep. For each sample, the network produced a value, *p*(N3), corresponding to the probability of N3 sleep.

Neural network training and testing

We trained the neural network on a dataset for 24 participants that included Fitbit data and sleep scores from an overnight session. Half of the participants were young adults who slept in the laboratory overnight for an unrelated study and half were middle-aged adults who slept at home. For the young adults, sleep stages were determined by manual scoring of PSG data; for middle-aged adults sleep stages were determined using the automatic scoring built into the Dreem 2.

Prior to training, we computed features for the Fitbit data as described above. To speed training, we subsampled the data by a factor of 5, to yield one sample every 5 s. Preliminary testing showed down-sampling did not meaningfully affect classifier accuracy, likely due to redundant information in successive samples. In total, 178,948 observations were included.

We then trained a perceptron neural network classifier with two hidden layers to predict whether each second would be scored as N3 based on the Fitbit features. Training was performed using the Neural module of JMP 15.2.1 (2019) using the 'squared' regularisation penalty. To evaluate the network's overall performance in classifying N3 sleep, we also trained a separate version of the model with one-third of the subjects (50,425 observations) held out from training as a validation set. The model achieved an area under the curve of 0.77 in classifying sleep as N3 or non-N3, indicating that it exceeded chance performance. We also evaluated alternative classifier schemes, including linear discriminant analysis and a convolutional neural network. Of these, the two-layer perceptron combined with our feature-extraction algorithm performed the best.

Automated TMR

Sounds were played at constant 10-s intervals (onset–onset), approximating TMR protocols used in laboratory studies where sounds were presented every 5–10 s (Creery et al., 2015; Rudoy et al., 2009; Whitmore et al., 2022). Sound presentation started when N3 sleep was detected, as operationalised by (a) a high value for the probability of N3 averaged over the most recent 240 s, *p*(N3) ≥0.9, and (b) the most recent value for *p*(N3) ≥0.85. Start/stop timing and sound intensity was controlled by the algorithm shown in Figure 3.

SleepStim was limited to presenting sounds when *p*(N3) was high within a time interval from 15 min to 3 h after the time the system was turned on. The system was also limited to stimulating for a maximum of 10.5 min. These constraints were imposed to minimise the chance of disrupting sleep and are consistent with protocols used in laboratory TMR studies (Rudoy et al., 2009).

Participants

We collected data from 120 adults recruited using flyers placed on campus. The protocol was approved by the Northwestern University Institutional Review Board. Participants provided written informed consent and were paid for their time.

We conducted three major analyses comprising (i) how frequently participants perceived TMR sounds, (ii) effects of TMR on memory, and (iii) EEG correlates of the TMR effect. All 120 participants were included in Analysis 1. For Analysis 2, we included only participants who completed memory tests and TMR stimulation in accordance with the protocol, as defined by the following criteria:

- Completion of training, the bedtime memory test, and at least one morning memory test.
- During sleep, at least 25 cues were presented.
- No more than four stimuli were presented when the Fitbit read a heart rate of zero (indicative of a poor heart rate signal).
- Objects were correctly allocated to cued and uncued conditions (which did not happen for three participants due to a bug in the allocation algorithm).

Analysis 2 included 61 participants, with a mean (SEM, range) age of 20.6 (0.23, 18–25) years and 17 (28%) were male.

Analysis 3 (EEG correlates of TMR) included 45 participants who met criteria for Analysis 2 and had at least 1 night of Dreem 2 data during cueing with sufficient quality for automatic sleep staging. These participants had a mean (SEM, range) age of 20.4 (0.24, 18–25) years and 14 (31%) were male.

Procedure

Day 1

Participants picked up the equipment and were instructed on the procedure and how to use the smartphone app. They wore the Fitbit and the Dreem 2 that night to allow for acclimation to the equipment. The phone played continuous white noise overnight. Participants used a slider in the app to set the white-noise intensity to a comfortable level. This intensity setting was used as the initial setpoint for sounds played during the night. Using the algorithm described in detail below, the app controlled presentation of a control sound (electronic ding) intended to help participants adapt to the potential disruption of sound presentations. The goal was to reduce sleep disruption from experimental sounds presented on subsequent nights. Targeting slow-wave sleep, the phone repeatedly played an electronic ding sound that was unrelated to the memory task.

Day 2

Using the phone, participants completed the learning phase at a mean (SEM) time of 10:24 p.m. (71 min). In this task (described in Figure 1b),

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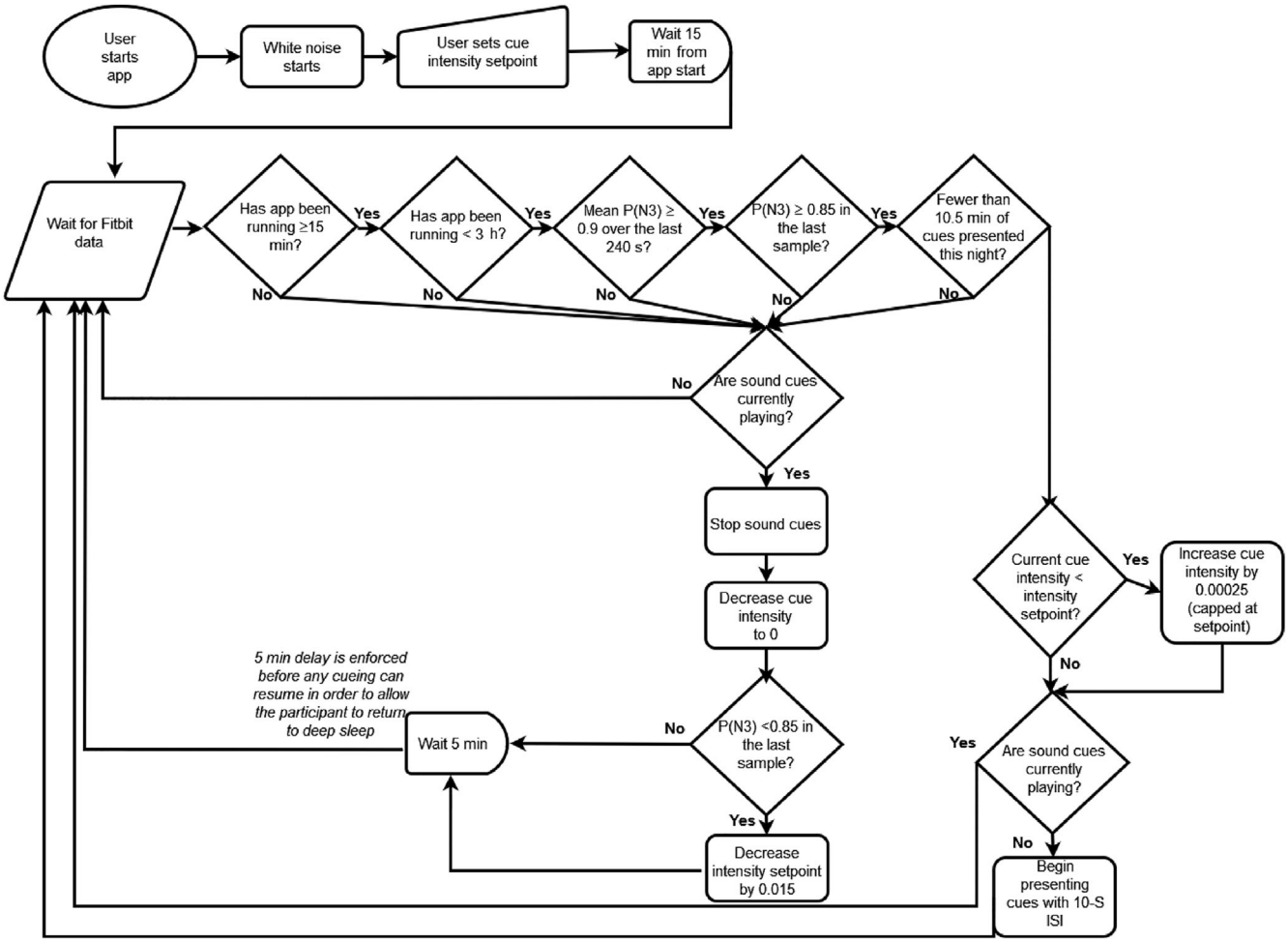

FIGURE 3 Flow chart illustrating how sounds are controlled in the SleepStim system. *p*(N3) is the probability that the participant is in N3 sleep as determined by the neural network classifier. The Fitbit transmits data once per second; if no Fitbit data is received for 10 s (indicating loss of signal), the sounds are turned off. A rapid drop in *p*(N3) while sounds are playing suggests the sounds aroused the participant and the auditory cue intensity may be set too high, therefore the auditory cue intensity setpoint is decreased if *p*(N3) drops below 0.85 while sounds are playing. Latency is approximately 1 s from acquisition to the availability of *p*(N3); the latency is constant and not affected by signal quality as data is never re-transmitted.

a grid covered the phone's entire screen, and participants learned the correct locations of objects on the grid. The app recorded accuracy and response times during each phase.

There were five blocks of trials, each with 10 objects. First, the participant was shown the correct locations of the 10 objects in that block. Then, each object appeared in the centre of the screen in a random order, and the participant attempted to move it to the correct location. The participant then received feedback consisting of a red X (if incorrect) or a green checkmark (if correct) at the location where they positioned the object. The feedback was presented for 2 s, after which the object was displayed in the correct position for 3 s. The placement was considered correct if the object was placed within 120 pixels (~2 cm) of the correct location; correct objects were dropped from the rotation. A block ended when the participant placed all objects correctly. The phone played the sound associated with each object when it first appeared on the screen, and when the correct location was shown in the feedback phase. The learning task was made unavailable after it was completed to ensure participants only completed it once.

Participants began the bedtime memory test shortly after completing the learning (mean [SEM] delay 11 [5] min). In this test, all 50 objects were presented sequentially in the centre of the screen, in random order, and the participant attempted to move each object to its correct location. Unlike in the learning phase, no feedback was given.

After participants completed their bedtime memory test, the app selected 25 objects to be cued during sleep using a matching algorithm to minimise the difference in bedtime memory performance between two sets of objects (to be cued and uncued). Objects were sorted by memory error and then assigned in alternating order (i.e., 1 = cued, 2 = uncued…). Because some differences remained after this assignment, the app also counterbalanced participants so that the assignment procedure started with cued in half of the participants and uncued in the other half. As expected, there was no difference in recall accuracy between cued and uncued objects in the bedtime memory test (Wilcoxon signed-rank test, $z[60] = 0.8$, $p = 0.42$).

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Shortly before going to sleep, the participant put on the Fitbit and Dreem 2, started the TMR app, and calibrated white-noise intensity. During the night, and on all subsequent nights, sounds linked to the 25 objects in the cued condition were presented during sleep.

Days 3 and 4

Participants completed a memory test in the morning. The test was identical to the memory test on Day 2, except with a different random order of objects. During sleep, they used the Fitbit, Dreem 2, and TMR app as on previous nights.

Day 5

Participants completed a final memory test in the morning and returned the equipment. When returning the equipment, we asked participants whether they remembered hearing any of the sounds from the memory task while they were sleeping. To avoid demand effects, participants were not asked about the TMR sounds (or told that TMR sounds were presented) until this point, consistent with laboratory TMR protocols.

Memory performance measurement

We measured *memory change* as the ratio of mean spatial error at a morning memory test to mean spatial error at the bedtime memory test (e.g., mean test1 error/mean bedtime test error). We computed this statistic separately for cued and uncued objects. We used non-parametric tests in comparisons of memory error as error values were not normally distributed (D'Agostino & Pearson, 1973).

For each test, we computed the *TMR effect* as the memory change for cued objects minus the memory change for uncued objects. A negative value indicates a benefit of TMR for memory. For example, a TMR effect of −0.1 implies that the increase in error for cued objects was 10% lower than the increase in error for uncued objects. We determined whether TMR effects differed significantly from zero using the Wilcoxon signed-rank test, a non-parametric one-sample test.

In the primary analysis of the TMR effect, we examined memory performance on the last test taken. Whereas participants were asked to take three memory tests, some failed to do so on one or more mornings. Therefore, our primary outcome was performance at *last* test, which was the last test for which data were available. For participants who completed all three tests ($n = 41$) we computed performance on each night.

Controlling for effects of initial memory performance

We observed that TMR effects were correlated with the pre-sleep difference in memory performance between cued and uncued objects (Figure 4), which could be interpreted as regression to the mean. That is, the larger the cued/uncued difference initially, the more likely this difference is reduced on the subsequent test. Because this effect adds variability that could obscure other correlations, we controlled for this effect before analysing relationships between the TMR effect and other variables. In this procedure, we used linear regression to isolate the relation between the TMR effect and initial memory performance differences between cued and uncued objects, computed separately for each test. The residual effect after covarying out the effects of initial performance was termed the *corrected TMR effect*.

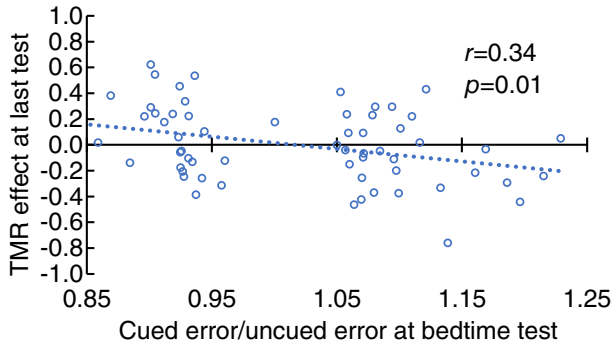

FIGURE 4 An example of the linear regression used to control for variation in memory performance in the bedtime test in Experiment 1. The bimodal distribution of bedtime test scores resulted from the procedure used to assign objects to cued and uncued conditions.

Dreem 2 sleep staging

We used data from the Dreem 2 headset to compute the time participants spent in each sleep stage, as well as the percentage of cues delivered in each sleep stage. Some participants did not have sufficient high-quality data for staging (by the proprietary Dreem 2 algorithm), so only a subset of 45 participants were included in these analyses.

EXPERIMENT 1 RESULTS

TMR cues were effectively targeted to N3 sleep

For 45 participants with EEG recordings of sufficient quality to permit sleep staging during cueing, we compared the percentage of cues delivered in each sleep stage to the percentage of overall time spent in that sleep stage. This analysis served as an independent test that the algorithm targeted N3 sleep in a new group of participants following the original test and validation set.

Results shown in Figure 5 revealed that SleepStim successfully targeted N3. Compared to the total time in each stage, the time when cues were played was more likely to be N3 ($t[44] = 3.56$, $p < 0.001$) and less likely to be classified as N2 ($t[44] = 2.26$, $p = 0.03$) or rapid eye movement (REM) sleep ($t[44] = 2.61$, $p = 0.01$). Although N2 was underrepresented in the cued sleep, a substantial number of cues were presented in N2 due to the higher base rate of N2 sleep. We did not observe differences between total sleep and cued sleep in wake

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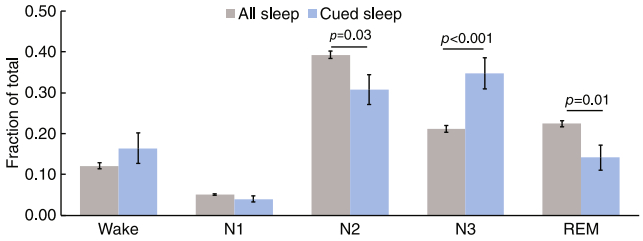

FIGURE 5 Results from Experiment 1 showing that the SleepStim system predominantly delivered cues during N3 sleep. Grey bars show the proportion of time spent in each sleep stage and blue bars show the distribution of sleep stages when cues were delivered. Whereas N3 comprised 21.1% of sleep, 34.7% of the cues were delivered in this stage, and 65.5% of the cues were delivered in stages N2 or N3. Cues in each stage are also listed in Table S1.

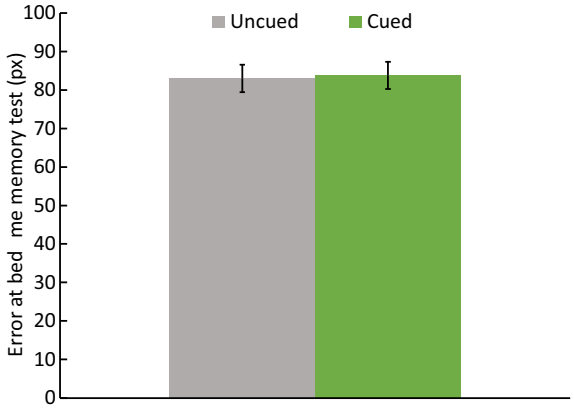

FIGURE 6 Error at the Experiment 1 bedtime test remained below the learning criterion (120 pixels). Error did not differ between cued and uncued conditions (Wilcoxon signed-rank test; mean difference = 0.76 pixels, $z(60) = 0.8$, $p = 0.42$). Individual participant values are shown In Figure S2.

or N1, which may be because these stages were rarely observed in the training set, providing little opportunity for the model to learn how to identify them.

Participants generally did not notice TMR cues

In the full sample (including participants who did not pass inclusion criteria), 16/120 participants (13%) reported hearing at least one sound from the memory task. No participants reported that the sounds disrupted their sleep or woke them. Among the participants included in analysis, seven of 61 (11%) reported hearing at least one sound.

Participants efficiently learned and retained object locations

Participants required a mean (SEM) of 1.61 (0.09) repetitions per object in the learning phase to reach criterion. In the bedtime test, participants' mean accuracy surpassed the criterion (Figure 6), indicating that the learning procedure created an effective memory at a short delay.

Recall accuracy declined but seemed uninfluenced by TMR

The mean (SEM) spatial error increased from 83 (3.51) pixels at bedtime test to 106 (3.90) pixels at last test, indicating significant forgetting (Wilcoxon signed-rank test; $z[60] = -6.27$, $p < 0.001$). No significant TMR effect was found at the last test or at any of the individual time points (Figure 7).

TMR effect was associated with cue-sound intensity and sleep-stage targeting

We hypothesised that sleep disruption caused by excessively loud cues might have reduced the benefits of TMR. Given previous findings that loud cues can disrupt memory processing in sleep (Whitmore & Paller, 2022), we quantified the maximum intensity used overnight. The memory benefit from TMR was significantly correlated with maximum auditory cue intensity and marginally correlated with the percentage of cues delivered in stage N3 (Figure 8, Table 1). That is, the tendency for memory to improve more for cued objects than for uncued objects was greater when intensity was lower and when more cues were delivered in N3.

Comparing TMR with optimal versus non-optimal parameters

Given these correlational results, we explored individual differences further by considering whether TMR might have a larger benefit in participants cued with optimal parameters, defined as receiving at least 25 sound cues on the adaptation night and using a relatively low maximum sound intensity (<0.02). We opted to select these participants because these two factors, adaptation procedures and sound intensity, could be directly controlled by the experimenter to reduce sleep disruption. Differences between the two groups were non-significant (Figure 9), but we did observe near-trend effects where the TMR effect was larger for the optimal-cued participants at last test (Mann–Whitney U test, $U[60] = 356$, $p = 0.12$) and at test 3 ($U[52] = 258$, $p = 0.11$). Neither the optimal or non-optimal group showed a significant effect of TMR at the last test or at test 3.

EXPERIMENT 2 METHODS

Because our initial experiment suggested that SleepStim could improve memory contingent on low auditory cue intensity, we conducted a follow-up study implementing an improved method. This experiment was identical to the original experiment, except for the following modifications.

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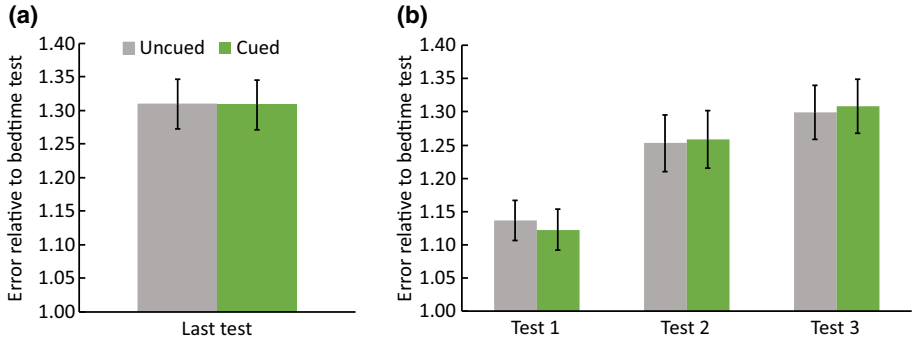

FIGURE 7 (a) Mean spatial error in Experiment 1 increased by ~30% for both cued and uncued objects at the last test (compared to the bedtime test immediately after learning). There was no significant difference in error between the cued and uncued objects. (b) in participants who completed all three morning tests ($n = 41$), error continued to increase throughout the experiment, reflecting forgetting. Error bars reflect the SEM for the within-subjects analysis of cued error-uncued error. Individual participant values are shown in Figure S2.

- Participants could not set initial intensity >0.02.
- A new algorithm required participants to receive at least 25 adaptation cues before they could begin the memory test, and if 25 cues were not presented, the adaptation procedure was administered again.
- Participants could receive up to 30 min of cueing per night (compared to 10.5 min in Experiment 1).
- We improved the algorithm for allocating objects to cued and uncued conditions, which matched conditions more closely, obviating the need for controlling for pre-sleep memory performance in the analysis.

Participants

Participants were recruited and paid using the same methods as the prior experiment. We collected data from 44 participants, and of these, 24 passed inclusion criteria and their data were included in the analysis of TMR effects on memory. Participants had a mean (SEM, range) age of 21.6 (0.65, 18–31) years and seven of the 24 (29%) were male.

EXPERIMENT 2 RESULTS

Participants rarely reported hearing sounds

In the full sample, four of 44 participants (9%) reported hearing TMR sounds during sleep. Among participants included in memory analysis, two of 24 (8%) reported perceiving TMR sounds. One of the two participants in the latter group who reported hearing sounds also reported that the sounds disturbed their sleep.

TMR improved spatial memory at last test

As shown in Figure 10, the improved TMR protocol significantly improved memory for cued objects relative to uncued objects at the last test (Wilcoxon signed-rank test; $z[23] = -2.69$, $p = 0.007$). For participants who took all three memory tests ($n = 18$), a significant

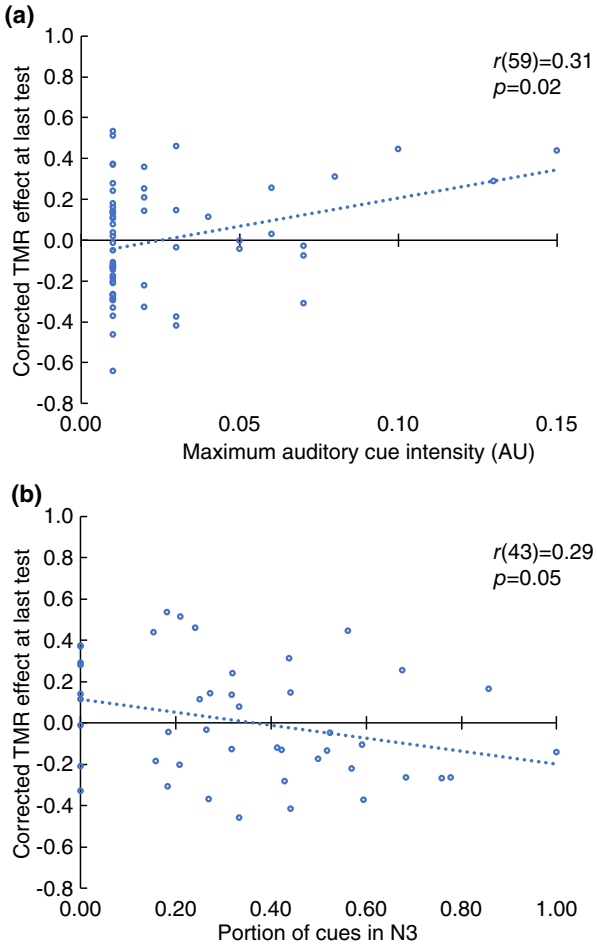

FIGURE 8 Correlates of the targeted memory reactivation (TMR) effect in Experiment 1. (a) Correlation between corrected TMR effect and maximum auditory cue intensity. (b) Correlation between corrected TMR effect and proportion of cues in N3. Corrected TMR effect is calculated as (cued error at last test/cued bedtime error) – (uncued error at last test/uncued bedtime error) - the TMR effect predicted from the bedtime test (Figure 4).

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TABLE 1 Correlations between the corrected targeted memory reactivation effect and sleep/participant variables in Experiment 1

Measure	Mean (SEM)	*p*	FDR *p*	*r*	Rationale
Total number of cues during experiment	145.13 (8.52)	0.36	0.77	−0.12	Increased number of cues may produce more reactivation and stronger effect
Cues per cued night	67.25 (3.25)	0.53	0.78	−0.08	Alternative measurement of the number of cues controlling the number of nights cued
Maximum cue intensity	0.03 (0.00)	0.02	0.25	0.31	Sound intensity is set by the user before sleep; excessively loud or soft cues might be ineffective
Number of sounds on adaptation night	48.23 (3.66)	0.26	0.65	−0.15	Receiving cues on the adaptation night might reduce sleep disruption on the first TMR night
Portion of sound cues delivered in N3	0.34 (0.04)	0.05	0.25	−0.29	Cueing in stages other than N3 might reduce the effects of TMR
Number of sound cues delivered in N3	17 (2.86)	0.05	0.25	−0.29	Cues might be especially effective in N3 sleep
Portion of sound cues delivered in N2 + N3	0.64 (0.04)	0.18	0.6	−0.2	Cues may work equally well in N2 and N3, but worse in other sleep stages.
Portion of sound cues in wake/N1	0.2 (0.04)	0.59	0.78	0.08	Cues in wake/N1 may be especially likely to be noticed and disrupt sleep.
Portion of sound cues in REM	0.14 (0.03)	0.20	0.6	0.20	Reactivation in REM may produce unique effects not seen in other sleep stages (Hutchison et al., 2021)
Portion of total sleep time in N3	0.25 (0.01)	0.57	0.78	0.09	Proxy for overall depth of sleep, which was shown to affect TMR in a previous study (Whitmore et al., 2022)
Portion of participants reporting hearing sounds	0.11 (0.04)	0.86	0.99	−0.02	In (Göldi & Rasch, 2019), participants who reported hearing cues had smaller TMR effects
Mean error at initial test (pixels)	83.39 (3.51)	1.00	1.00	0.00	TMR effects may depend on the strength of initial learning (Creery et al., 2015)
Morning memory tests performed	2.87 (0.05)	0.61	0.78	0.07	If TMR effects evolve over time, participants who completed all tests might show a different effect than those completing only some tests
Number of nights cued	2.18 (0.11)	0.62	0.78	−0.06	Repeated cueing on multiple nights may increase the total reactivation and provide a stronger TMR effect
Participant age in years	20.56 (0.23)	0.92	0.99	−0.01	Previous studies (Cordi et al., 2018; Whitmore et al., 2022) found TMR effects were associated with age

Abbreviations: FDR, false discovery rate; REM, rapid eye movement; TMR, targeted memory reactivation.
Note: Correlation is a linear regression. Sign of the *r* value indicates the direction of the correlation; a negative *r* indicates higher values of the independent variable are associated with more benefits of TMR for memory. Statistics are calculated using the 61 participants included in the memory analysis, except for correlations with time in sleep stages that were performed in the subset of 45 participants with scorable electroencephalography. Corrected TMR effect is calculated as (cued bedtime error/cued error at last test) – (uncued bedtime error/uncued error at last test) - the TMR effect predicted from the bedtime test (Figure 3). We identified correlates of TMR effect using the non-FDR-corrected *p* values, as this analysis was an initial screen followed up with a separate experiment, the less conservative approach is most appropriate.

difference between cued and uncued conditions emerged at the second memory test and persisted in the third test (Wilcoxon signed-rank test; $z[17] = -1.63, -2.24, -2.29$, $p = 0.103$, $p = 0.025$, and $p = 0.022$ for test 1, 2, and 3, respectively).

DISCUSSION

Given that studies in the home environment would greatly expand research and applications related to memory processing during sleep, we designed and tested SleepStim, a novel wearable system for presenting auditory cues during sleep. In Experiment 1, we found that cues did not improve memory overall, but across participants the memory effect was correlated with auditory cue intensity. We limited auditory cue intensity in Experiment 2 and found that cues benefitted memory. Our results confirmed that SleepStim can target deep sleep and produce memory benefits that mirror those achieved via memory reactivation in sleep laboratories equipped with PSG equipment. We used a wearable device for obtaining EEG data from the forehead to validate our procedure, but the TMR method we devised can be applied with this system using only a wrist-worn device and a smartphone, making it easy to use, efficient, relatively inexpensive, and well tolerated by most individuals. The results demonstrate that home sleep interventions with the SleepStim system are feasible and effective, provided that adequate consideration is given to avoiding arousal.

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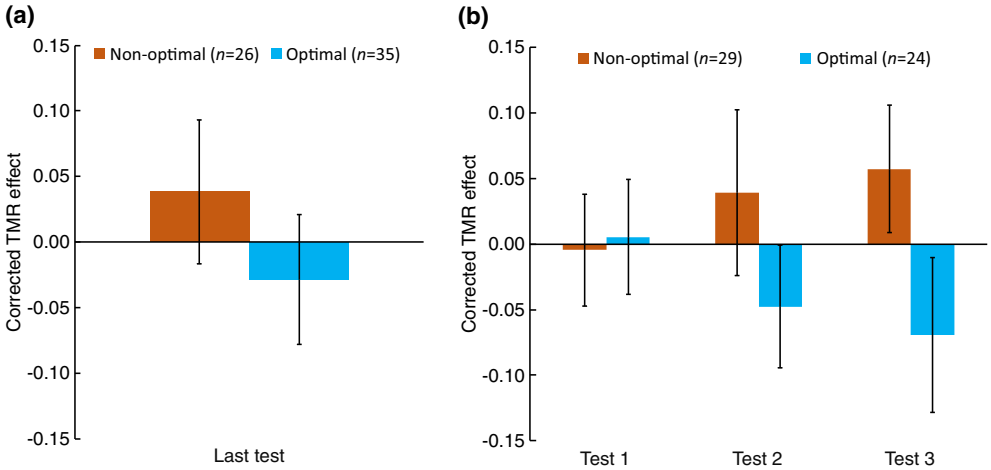

FIGURE 9 In Experiment 1, participants cued with optimal parameters appeared to diverge from those cued with non-optimal parameters. Results are shown for participants on their last test (a) and for all three tests (b). Corrected TMR effect is calculated as (cued error at last test/cued bedtime error) – (uncued error at last test/uncued bedtime error) – the TMR effect predicted from the bedtime test (Figure 4). Individual participant values are shown in Figure S2.

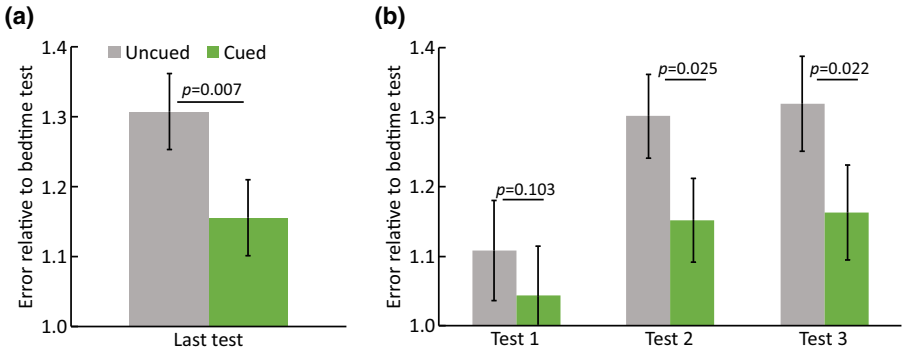

FIGURE 10 Experiment 2 results. (a) Targeted memory reactivation (TMR) effects at the final memory test. (b) TMR effects at each time point, for the participants who performed all three morning memory tests. Error bars reflect the SEM for the within-subjects analysis of cued error versus uncued error. Figures S1 and S2 show data for individual participants.

An important finding in our experiment was that participants remained unaware that TMR cues were presented in almost all cases, with 13% of all participants (11% of those included in memory analysis) reporting hearing cues in Experiment 1 and 7% (8% of those included in memory analysis) reporting cues in Experiment 2. Rates of cue perception did not significantly differ between the two experiments. Low cue perception rates are a substantial improvement over brain-state independent home TMR in past studies in our laboratory and others, where participants frequently reported hearing cues and having their sleep disturbed (e.g., Göldi & Rasch, 2019). Presenting cues without participants noticing is important for usability and to avoid accidentally unblinding participants in experiments where they are assigned to different conditions. This result also confirms that SleepStim can target states where participants are soundly asleep.

The ability to target deep sleep was also reflected by analysis of the times of cue delivery in relation to the automatic sleep staging provided by Dreem 2. Cues were delivered disproportionately in N3 sleep, and most of the cues not delivered in N3 were delivered in N2. In a recent meta-analysis of the TMR literature, memory benefits were found for both N2 and N3 sleep (Hu et al., 2020). In TMR experiments aimed at enhancing memory in the sleep laboratory environment, cues are typically presented in either N3 or a combination of N2 and N3, and memory-related sleep features like spindles and slow waves occur in both of these stages (Dijk et al., 1993). Our results show that SleepStim can target deep non-REM sleep and deliver cues without waking participants, both important advances for sleep-intervention studies in the home. Our findings also showed that better targeting of N3 was associated with stronger benefits of TMR for memory (Figure 8b), further emphasising the importance of targeting cues to N3.

Despite the system's overall ability to target N3, ~16% of cues were delivered in wake as determined by the Dreem 2 algorithm. The cueing procedure may not have avoided wake epochs as intended. Perhaps the machine learning was imperfect, in that neural networks can function unpredictably when provided with data outside the domain of their training (Tsimenidis, 2020); the low amounts of wake and N1 recorded in the training set may have provided insufficient training. Similarly, wake movement patterns recorded in a sleep laboratory likely differ from those at home. Wake cueing could be reduced by adding additional constraints such as not cueing immediately after significant body motion.

We demonstrated that the TMR procedure at home can yield the typical effect observed in the laboratory, where TMR with quiet sounds improves performance in a spatial memory task (Antony et al., 2018; Creery et al., 2015; Rudoy et al., 2009; Schechtman et al., 2021; Vargas et al., 2019). We also found that loud cues reversed the TMR effect, consistent with our prior findings in a study of face-name learning (Whitmore & Paller, 2022). Accordingly, our findings suggest that home TMR can be useful for investigating memory and perhaps in clinical applications as well. In particular,

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TMR at home may open up possibilities for clinical research with TMR, studies of performance enhancement over multiple nights, and TMR studies with larger numbers of participants and greater efficiency.

Our results also highlight the critical importance of auditory cue intensity and sleep disruption in home TMR. In Experiment 1, we attempted to control sleep disruption through two strategies. First, initial auditory cue intensity was at the white-noise level that participants set before sleep. Second, auditory cue intensity was decreased upon detection of a cue-evoked arousal. Our analysis revealed that participants who set a high intensity almost always showed a reversed TMR effect, indicating that participants' intensity settings were generally not optimal. Because very few participants reported hearing cues, the reversed TMR effect likely resulted from micro-arousals rather than full awakenings. Therefore, we opted to strictly limit intensity in Experiment 2. Our recommendation is that cues for home TMR be barely audible in a quiet room. Optimising methods for calibrating intensity and making adjustments during the night is an important challenge for future research.

The goal of this study was to test whether TMR could be effective in a home environment. The limitations included the absence of objective measures of sleep quality from PSG. Sleep measures were based on Dreem 2 algorithms; while we did not evaluate agreement with a second human scorer (as is typical in laboratory studies), the Dreem 2 has previously demonstrated high agreement with human scorers (Arnal et al., 2020). The SleepStim system may be less effective at targeting N3 than a human operator. Also, participant behaviour was less standardised than in many laboratory studies. We deliberately opted not to control factors like bedtimes or stimulant/alcohol use, given our goal was of examining TMR in a naturalistic setting. Despite these limitations, we found that data acquired with our SleepStim-based protocol replicated typical effects of TMR with improved memory for reactivated items.

Currently there remain many unanswered questions about factors that influence TMR efficacy. For example, do different cueing strategies (such as cues at random versus regular intervals) produce different effects on memory? The ability to run high-throughput TMR experiments at home may facilitate research on such questions. SleepStim offers a powerful platform for future sleep research. The ability to run TMR experiments at scale outside the sleep laboratory can enable new fundamental and clinical studies. The ability to deliver closed-loop interventions in sleep using SleepStim may also be useful for applications beyond TMR, such as influencing dream content (Konkoly et al., 2021) or non-phase-locked entrainment to increase slow wave and spindle activity (Antony & Paller, 2016; Simor et al., 2018).

AUTHOR CONTRIBUTIONS

Nathan W. Whitmore and Ken A. Paller designed the experiment. Nathan W. Whitmore collected, analysed, and interpreted data and wrote software. Torin Kovach and Jasmine C. Harris wrote software. Ken A. Paller supervised the project. Nathan W. Whitmore wrote the manuscript with input from Ken A. Paller.

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CONFLICT OF INTEREST

All authors declare that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in OSF at http://doi.org/10.17605/OSF.IO/6MQK2. Code and documentation for the SleepStim system is available at https://github.com/nathanww/home-tmr.

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