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Shaping memory consolidation via targeted memory reactivation during sleep

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RUNNING HEAD: Shaping Memories During Sleep

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Abstract

Recent studies have shown that the reactivation of specific memories during sleep can be modulated using external stimulation. Specifically, it has been reported that matching a sensory stimulus (e.g., odor or sound *cue*) with target information (e.g., pairs of words, pictures, motor sequences) during wake, and then presenting the *cue* alone during sleep, facilitates memory for the target information. Thus, presenting learned cues while asleep may reactivate related declarative, procedural and emotional material, and facilitate the neurophysiological processes underpinning memory consolidation in humans. This paradigm, which has been named *targeted memory reactivation* (TMR), has been successfully used to improve visuospatial and verbal memories, strengthen motor skills, modify implicit social biases and enhance fear extinction. However, these studies also show that results depend on the type of memory investigated, the task employed, the sensory cue used, and the specific sleep stage of stimulation. Here we present a review of how memory consolidation may be shaped using non-invasive sensory stimulation during sleep.

1 Introduction

Memory formation comprises at least three different sub-processes: acquisition of information (encoding), reorganization of this information for long-term storage (consolidation) and recall of the learned material (retrieval). During consolidation, newly acquired memories need to be processed and integrated with existing information in order to become stable and less susceptible to interference.¹ Successfully stored information can then be accessed and recalled. An optimal condition for memory consolidation is sleep, where external input is reduced and the brain experiences different states that seem to facilitate the memory process.^{2,3}

According to the *two-stage model of memory trace formation*,^{4,5} information is initially encoded in parallel in cortical networks and in the hippocampus. During subsequent non-rapid movement sleep (NREM, which is composed of stages N1-3, the latter also known as slow wave sleep, SWS) these memory traces are repeatedly re-activated, reorganized and consolidated into cortical networks, creating persistent traces independent from the hippocampus.^{6,7}

Consistent with this idea, compelling evidence has shown that recent memories are “replayed” during sleep. For example, a seminal paper by Wilson and McNaughton⁸ showed that the temporal sequence of place-cell firing activity of rats exploring a maze was “replayed” during the subsequent sleep. Similarly, during sleep, birds replay the neuronal activity involved in song-learning during wakefulness.⁹ In humans, it has been observed that the same brain regions engaged during task-learning are reactivated during the subsequent sleep period.¹⁰⁻¹² These findings converge toward a key role of trace reactivation during sleep in the consolidation of memories.

Physiological mechanisms of memory consolidation during sleep.

According to the *active system consolidation model* (ASC),^{1,7} which is based on the *two-stage model of memory trace formation*,^{4,5} optimal memory consolidation may depend on the temporal coupling of cortical slow oscillations (SO; waves of .5-1Hz and amplitude $\geq 75\mu V$), thalamic sleep spindles (short bursts of oscillatory activity in the frequency range of 9–16Hz originating in the reticular thalamus), and hippocampal sharp-wave ripples (SWR; transient excitatory bursts of about 200Hz originating in the hippocampus CA1 region). During NREM sleep, SO synchronize neuronal activity both in the neocortex and in other regions relevant to memory consolidation such as the thalamus and the hippocampus, where thalamocortical spindles and SWR originate, respectively.¹³⁻¹⁵ Thus, SO may provide a global temporal frame whereby the depolarizing up phases repeatedly drive the reactivation of memories in hippocampal circuits in parallel with thalamocortical spindles, enabling these signals to reach the neocortical networks while still in the depolarizing up-state.¹⁶ The memory traces are also locally potentiated by sleep spindles, which seem to induce local plasticity in selected neuronal circuits that were previously reactivated.¹⁷ Consolidation seems to continue across subsequent rapid eye movement (REM) sleep, where the higher levels of acetylcholine, compared to NREM and wake,¹⁸ allow for the induction and maintenance of long-term potentiation, supporting the strengthening of memory representations at the synaptic level.^{1,19} This highly plastic state has been associated with integrating newly acquired memories with older associations,²⁰ enhancing previously learned skills,²¹ and rescuing new memories from interference.²²

Another influential theory, the synaptic homeostasis hypothesis (SHY),³ proposes that encoding of information during wakefulness produces progressive synaptic strengthening. This synaptic potentiation increases energy and nutrients demands, reduces extracellular space, the selectivity of neuronal responses and the signal to noise ratio, and saturates the ability to learn, resulting in a progressive impairment of cognitive functions. However, during sleep, the synaptic strength is reduced (i.e., down-scaled) via slow wave activity (SWA, .5-4.5Hz, but see also²³ for a potential role of REM sleep in the synaptic downscaling process). Since strongly potentiated synapses are relatively more protected from downscaling than weak synapses, this process facilitates memory consolidation by increasing the signal to noise ratio. Moreover, this process is purported to restore the neuronal selectivity and the ability to learn new information. Recently, it has been proposed that

the two models can be integrated,^{17, 24-26} a viewpoint that suggests that local memory potentiation and global downscaling work synergistically to optimize memory processes.

Playing with Memory During Sleep: The Targeted Memory Reactivation Paradigm

Studies in both humans²⁷ and animals²⁸ have shown that reactivation of specific memories during sleep can be modulated using external stimulation. Specifically, it has been observed that matching a sensory stimulus (e.g., odor or sound *cue*) with target information (e.g., pairs of words, objects, motor sequences), and then presenting the *cue* alone during sleep, facilitates the neurophysiological processes (e.g., coordination of sleep spindles and SO) underpinning memory consolidation. Thus, presenting learned cues while asleep seems to be able to reactivate related (i.e., *cued*) declarative, procedural and emotional material. This paradigm, named *targeted memory reactivation* (TMR), has been successfully used to improve visuospatial¹¹ and verbal memories,²⁹ strengthen motor skills,³⁰ modify implicit social biases³¹ and enhance fear extinction (see Ref. 32; Fig.1). However, these studies also show that results depend on the type of memory investigated, the task employed, the sensory cue used, the timing of the cue delivery and the specific sleep stage of stimulation.

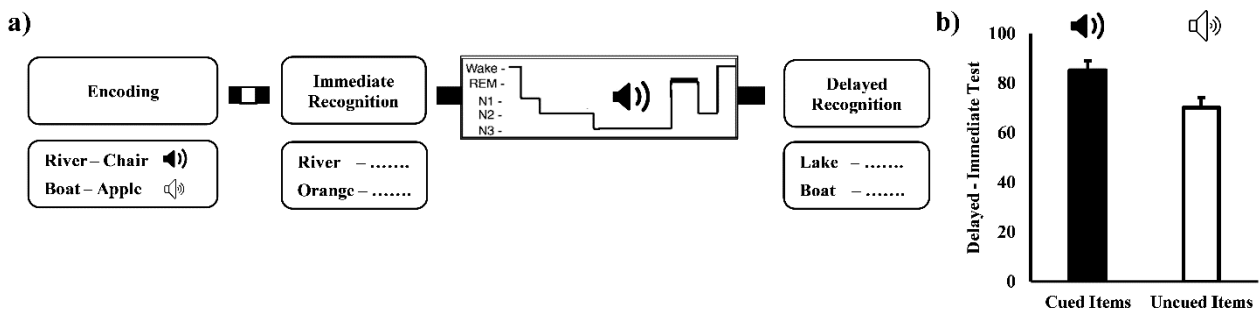


Figure 1. Schema of a targeted memory reactivation (TMR) paradigm. **a)** During the encoding phase, participants learn some material (e.g., unrelated pair of words). Items are associated with some sensory cue(s) (e.g., semantically related sound cues). Then, they perform an immediate memory test (e.g., a cued-recall task) followed by a period of sleep (or wake). During specific sleep stages (i.e., N2, N3, REM), one (or more) of the associated cue(s) is presented several times. After the sleep period, a delayed test is performed. **b)** Example of a typical TMR result. Performance is often computed as the change between the immediate and the delayed tests as a function of the condition (Cued vs Uncued items). Cued items (items whose associated cue was presented during sleep) are remembered better than uncued items (items whose associated cue was not presented during sleep).

Here, we will review the effects of TMR for different memory domains (declarative, procedural, emotional, see also Table 1), discussing strengths and weaknesses of different protocols and the efficacy of the various sensory stimulations (olfactory, auditory). We will also discuss other exciting paradigms that use sensory stimuli via *close-loop stimulation* or *rhythmic auditory sequences* to shape memory consolidation, and can be combined with TMR protocols.

Table 1. Main information of targeted-memory reactivation studies presented in this review.

Study	Cognitive domain	Task	Type of cue	Effect of TMR	Neural correlates of TMR during sleep
Rasch et al. 2007 ¹¹	Visuo-spatial memory	2-D object location	odor	+	↑ Hippocampal activity
Rasch et al. 2007 ¹¹	Procedural memory	MSL	odor	=	↑ Hippocampal activity
Diekelmann et al., 2011 ³³	Visuo-spatial memory	2-D object location	odor	+	↑ Hippocampal activity
Diekelmann et al., 2012 ³⁴	Visuo-spatial memory	2-D object location	odor	+	N/A
Rihm et al., 2014 ³⁸	Visuo-spatial memory	2-D object location	odor	+	↑ Frontal delta, ↑ Parietal fast spindles
Klingzing et al., 2017 ³⁹	Visuo-spatial memory	2-D object location	odor	+	N/A
Cordi et al., 2014 ³⁵	Visuo-spatial memory	2-D object location	odor	+	N/A
Seibold et al., 2017 ³⁶	Visuo-spatial memory	2-D object location	odor	+	N/A
Rudoy et al., 2009 ⁴⁰	Visuo-spatial memory	Object location	odor	+	↑ Overall EEG amplitude
Van Dogen et al., 2012 ²⁷	Visuo-spatial memory	Object location	auditory	+	↑ Parahippocampal activity, ↑ Functional connectivity between hippocampal and occipital areas
Oudiette et al., 2013 ⁴⁴	Visuo-spatial memory	Object location	auditory	+	↑ Frontal delta
Creery et al., 2015 ⁴²	Visuo-spatial memory	Object location	auditory	+	↑ Frontal delta
Cairney et al., 2016 ⁵⁰	Visuo-spatial memory	Object location	auditory	+	N/A
Cairney et al., 2016 ⁵⁰	Declarative memory	Picture-word associations	auditory	+	N/A
Oyarzun et al., 2017 ⁴⁹	Visuo-spatial memory	Object location	auditory	+	↑ Theta and beta activity
Schreiner & Rasch, 2014 ⁵³	Vocabulary	Language learning	auditory	+	↑ Theta activity
Schreiner & Rasch, 2015 ⁵⁴	Vocabulary	Language learning	auditory	+	↑ Theta and spindles activity
Batterink & Paller, 2015 ⁵⁷	Vocabulary	Artificial grammar learning	auditory	+	N/A
Batterink et al., 2017 ⁵⁸	Vocabulary	Novel words learning	auditory	+	N/A
Tamminen et al., 2017 ⁵⁹	Vocabulary	Mental lexicon	auditory	+	N/A
Donohue & Spencer, 2012 ⁶⁰	Declarative memory	Word-pairs associations	auditory	-	N/A
Fuentemilla et al., 2013 ⁵¹	Declarative memory	Word-pairs associations	auditory	-	N/A
Cairney et al., 2017 ⁵⁰	Declarative memory	Word-sound associations	auditory	+	N/A
Groch et al., 2017 ⁵²	Declarative memory	Picture-word associations	auditory	+	↑ Theta and spindles activity
Groch et al., 2017 ⁸⁴	Declarative memory	Picture-word associations	auditory	+	N/A
Farthout et al., 2016 ⁵⁶	Declarative memory	Word-sound associations	auditory	=	↑ Theta and spindles activity
Hennies et al., 2017 ⁶¹	Declarative memory	Statistical regularities	auditory	-	N/A
Laventure et al., 2016 ⁶⁷	Procedural memory	MSL	auditory	+	↑ Spindle activity
Pereira et al., 2017 ⁷⁰	Procedural memory	MSL	tactile	=	↑SO, ↓spindles
Antony et al., 2011 ³⁰	Procedural memory	SRTT	auditory	+	N/A
Schonauer et al., 2014 ⁷¹	Procedural memory	SRTT	auditory	+	N/A
Cousins et al., 2014 ⁷²	Procedural memory	SRTT	auditory	+	N/A

Cousins et al., 2016 ⁷³	Procedural memory	SRTT	auditory	+	N/A
Diekelmann et al., 2016 ⁷⁴	Procedural memory	SRTT	odor	=	N/A
Johnsen et al., 2017 ⁷⁵	Procedural memory	Throwing task	auditory	+	N/A
Honma et al., 2016 ⁹⁵	Body perception	Rubber-hand illusion	auditory	+	N/A
Ritter et al., 2012 ⁹³	Creativity	Unusual use task	odor	+	N/A
Hu et al., 2015 ³¹	Implicit associations	IAT	auditory	+	N/A
Cairney et al., 2015 ⁸⁰	Emotional memory	Emotional pictures	auditory	+	↑ Spindle number
Sterpenich et al., 2014 ⁸¹	Emotional memory	Emotional pictures	auditory	+	N/A
Ashton et al., 2017 ⁸³	Emotional memory	Emotional pictures	auditory	=	N/A
Lehman et al., 2016 ⁸²	Emotional memory	Picture-word associations	auditory	+	N/A
Groch et al., 2017 ⁹²	Declarative memory	Picture-word associations	auditory	+	N/A
Rihm et al., 2016 ⁹¹	Emotional memory	Pictures evaluation	odor	=	↑ Spindle activity
Hauner et al., 2013 ⁸⁵	Fear memory	Fear conditioning	odor	+	↑ Hippocampal and amygdala activity
Ai et al., 2015 ⁸⁸	Fear memory	Fear conditioning	auditory	+	N/A
He et al., 2015 ⁸⁶	Fear memory	Fear conditioning	auditory	+	N/A
Rihm & Rasch, 2015 ⁸⁷	Fear memory	Fear conditioning	odors	+*	N/A

Notes. SRTT: Serial Reaction Time Task. IAT: Implicit Association Task. MSL: Motor Sequence Learning. N/A: No correlates. +: positive TMR effect. =: no TRM effect. -: negative TMR effect. * TMR modulates emotional tone but not memory performance.

TMR and declarative memory

Visuo-Spatial Memory

In a seminal study, Rasch and colleagues¹¹ showed that olfactory stimulation during SWS improved visuospatial memories. Specifically, a group of participants performed a 2-D object-location memory task, in which they had to learn the location of 15 pairs of cards representing animals or everyday objects arranged in a 5x6 checkerboard-like grid. Each card was presented for one second followed by the card-pair presented to the participants for three seconds. Then, cards were turned on their back. This was followed by a cued recall test, in which the first card of each pair was presented and the participants had to indicate the location of the second card-pair. The authors observed that when a context odor (the scent of a rose) was delivered via nasal mask during the presentation of the card-pairs, and then presented again during subsequent SWS, participants showed better performance (i.e., less forgetting) compared to the following control conditions: 1) odorless vehicle delivered during sleep, 2) no odor presented during learning, 3) odor delivered during REM sleep, and 4) odor delivered during a post-learning wake period. Notably, the authors also reported that re-exposure to the context odor during SWS was associated with activation of the anterior and posterior hippocampus (observed using functional magnetic resonance imaging) to a greater extent than exposure to the odor while awake. These results were confirmed by Diekelmann and colleagues³³, who showed that memory traces reactivated during sleep became more stable and resistant to subsequent interference learning (e.g., learning new card-pair locations). Interestingly, they also observed the opposite effect when the context odor was delivered during wakefulness- destabilization of these memories and increased sensitivity to interference. In a subsequent study,³⁴ the same research group investigated the extent of these beneficial effects of odor-induced TMR, showing that reactivation during a 40-min period of sleep promotes the same amount of performance improvement as a 90-min sleep period without any stimulation. Interestingly, in the 90-min sleep without odor stimulation condition, the improvement was positively associated with the amount of SWS, in line

with literature indicating that declarative memory consolidation is specifically associated with neural activity in this sleep stage [see Ref.1]. Thus, the results of this study suggest that endogenous sleep-related memory consolidation processing can be accelerated by sensory stimulation.

Cordi and colleagues³⁵ focused on TMR during REM sleep, and replicated the finding that memory stability is not affected by olfactory TMR during this stage. Specifically, odor and vehicle control stimulation during REM sleep produced the same performance outcome. Moreover, performance outcomes for both these conditions was decreased compared to TMR during SWS,³³ suggesting that TMR is beneficial only when performed in SWS. The same group further tested the relationship between TMR and interfering memories.³⁶ Specifically, they asked participants to learn a series object-location pairs while an odor was presented (Day 1). Twenty-four hours later (Day 2), participants were asked to learn a different set of object-location pairs with no odor pairing. During the following sleeping period, either the Day 1 odor or an odorless vehicle was delivered during SWS. After about 40 minutes of SWS they were awakened and tested on the object-location task encoded on Day 2, and then on the object-location task encoded on Day 1. Contrary to the authors' hypothesis, the context odor (associated with Day 1 task) did not impair the consolidation of the Day 2 task, but rather promoted its stabilization (i.e., there was lower "intrusion" from the Day 1 task compared to the vehicle stimulation condition). The authors speculated about this counterintuitive effect, suggesting that perhaps memory of the Day 1 task, encoded 24hrs before, was too weak to be reactivated during Day 2 sleep, or that the context odor could have also been associated with the Day 2 task due to the similarity of the two tasks, thereby promoting the stabilization of the Day 2 memories with the Day 1 odor. This idea leads to an interesting hypothesis: olfactory TMR may also promote the stabilization of information semantically or conceptually-related to the cued-memory.

Overall these results suggest that context olfactory stimulation can facilitate memory consolidation of visual-spatial information, probably due to fact that odor information is directly relayed from the olfactory bulb to the hippocampus and the amygdala.³⁷ However, this facilitative effect is only observed when the stimulation is performed during SWS. However, although two studies showed that odor-stimulation increased hippocampal activity during sleep,^{11, 33} no direct correlation between cue-induced hippocampal activity and the observed TMR benefit was reported. Thus, these results may only indirectly support the idea that TMR can promote memory reactivation. Also, another limitation of these studies was that they did not address the question of specificity of the olfactory stimulation (i.e., whether the improvement is observed only when the same odor presented during learning is represented during sleep or whether a different odor can induce the same behavioral outcome). Rihm and colleagues³⁸ tried to disentangle this question. Their results showed a memory improvement only when the participants were exposed to the context odor during SWS, whereas presenting a non-context odor (i.e., an odor which was not matched with the learning material during the encoding phase) or an odorless vehicle stimulation resulted in a lower number of card-pairs remembered. Context stimulation during sleep also affected the sleep EEG activity. Specifically, authors observed an increase in EEG power in frontal delta (1.5-4.5Hz) and parietal fast spindles (13-15Hz), two EEG activities purported to coordinate the reactivation and consolidation of declarative from the hippocampus to the cortical networks.^{2, 17} Interestingly, it has been recently suggested that the beneficial effect of olfactory-induced TMR seems not to rely on the same neurophysiological mechanism underlying neural reactivation during sleep.³⁹ Indeed, a recent pharmacological study observed a benefit of odor stimulation during SWS even when the cholinergic tone of the participants was increased using physostigmine, an acetylcholinesterase-inhibitor that effectively increases the accumulation of acetylcholine at the synaptic level.³⁹ These results was surprising, since the authors expected that physostigmine would block hippocampal-neocortical communication (i.e., systems consolidation). This finding challenged the idea that TMR promotes the direct redistribution of information from the hippocampus to the neocortex. Rather, as suggested by the authors, TMR may strengthen the visual-spatial memory directly at the hippocampal level, and thus indirectly facilitating the subsequent reactivation.

All in all, these studies indicate that re-exposure to an odor previously associated with items to be remembered during SWS (but not during REM or during wakefulness) facilitates the stabilization of these memories, making them resistant to interference. Moreover, the presentation of olfactory cues modulates hippocampal activity during sleep, although no causal association between increased neural activity due to the odor presentation and improved memory consolidation can be drawn from these studies. Another limitation of these studies, mainly due to the constraints of the olfactory system, is that they targeted a large set of stimuli, but they were not able to cue individual items in order to assess the specificity of the purported reactivation process. This limitation has been overcome by another line of research, which uses auditory stimuli as sensory cues to selectively cue a subset of the stimuli during sleep by matching each item with a unique sound.

In the first study to use auditory cueing, Rudoy and colleagues⁴⁰ asked participants to learn the location of 50 pictures of animals/objects displayed on a computer screen. Each picture was presented individually for a few seconds in a unique position on the screen and paired with a unique sound (e.g., a picture of lightning paired with the sound of thunder, and a picture of a cat with *meow*). After the learning phase, participants took a daytime nap and the sounds of half of the objects were presented during NREM sleep (during both N2 and SWS) via speakers. Following the nap, participants were tested on the location of each of the 50 objects. The results showed that participants were more accurate for objects whose corresponding sound was presented during sleep (*cued items*) compared to objects whose associated sounds were not presented during sleep (*uncued items*). This effect was not observed when the auditory stimulation was performed during a post-learning wake period, indicating that this auditory TMR is sleep-dependent and sound-specific. The same object location task was used by Van Donger and colleagues,²⁷ who tested the effect of the sound-induced reactivation while participants were sleeping in an MR scanner, in order to assess blood oxygen level dependent (BOLD) activity and functional connectivity during sound presentation. They failed to replicate the beneficial effect of acoustic stimulation on behavioral performance observed by Rudoy and colleagues.⁴⁰ However, at the neural level, the authors observed increased BOLD activation in parahippocampal cortex, and increased functional connectivity between this area and posterior brain regions, including visual areas, during the presentation of acoustic cues. Moreover, they observed a positive association between brain activity during acoustic stimulation (in the thalamus, hippocampal and parahippocampal areas), and subsequent behavioral performance. These data were further explored using graph-theory analysis,⁴¹ which showed that acoustic stimulation induced increased network integration (i.e., increased connectivity within a specific brain network) in the occipital cortex. These findings suggest that, notwithstanding the lack of memory benefit, the acoustic presentation induced changes in brain memory regions.

These observed differences in the behavioral outcomes may be due to individual differences, as suggested by another study.⁴² Using the same auditory-cueing paradigm as the two previous studies, the authors observed that TMR enhanced sleep-related consolidation, but this effect was mediated by the initial level of encoding. Specifically, better pre-sleep performance was associated with greater TMR benefit observed at the post-sleep test. Conversely, lower performance at the pre-sleep test was associated with reduced TMR benefit at the post-sleep test. The authors suggested that TMR can also reactivate memories mistakenly encoded (i.e., a wrong location of an object). Therefore, it is possible that an incorrect application of TMR may be detrimental, leading to the consolidation of erroneous or unwanted memories. Opposite findings were reported by Cairney et al.,⁴³ who used a modified version of the same task to assess the effect of TMR with stimuli directly (i.e., sounds semantically-related with a picture) or indirectly (i.e., sounds not semantically-related with a word) associated an acoustic cue. They observed a beneficial effect of TMR only on directly associated memories, but, contrary to Creery et al.,⁴² this effect was stronger for stimuli that were initially weakly encoded. The authors suggested these differences could be due to differences in the experimental procedure (e.g., different delay between training and test).

Oudiette et al.,⁴⁴ further expanded this line of research using another modified version of this task to test whether TMR could benefit the consolidation of information of different “values”. Indeed,

previous studies showed that sleep preferentially benefits rewarding information.⁴⁵⁻⁴⁸ The authors manipulated the stimuli adding to each object a number which represented the “value” of the item. They first confirmed previous findings of a greater sleep benefit for high-value items compared to low-value items, and then tested if TMR applied to these items could rescue low-value item from forgetting. They observed that low-value items were indeed remembered better after TMR compared to a no-stimulation condition, but no difference was observed between cued and uncued items. The authors suggested that the stimulation of some low-value items could have led to a generalized reactivation for the whole category of low-value items. More recently, Oyazun and colleagues⁴⁹ used the same visuospatial location task to test the effect of TMR on overlapping memories. Specifically, participants had to initially learn the location of 15 card-pairs (set X1-X2) and after 5 minutes (contiguous condition) or 3 hours (delayed condition), they were asked to encode the location of a second set of 15 card-pairs (set X1-X3). In the second set, the first card (X1) of each pair was positioned in the same location as in the first set, while the location of the second card was different, creating overlapping events. Also, during the encoding of the second set, each card-pair was associated with a distinct sound, which was then presented during the subsequent nap. After the nap participants were tested on the first set (X1-X2). The authors showed that on the one hand, TMR improved the consolidation (i.e., the percentage of correct locations identified) of information in the contiguous condition (when the two sets were encoded one after the other), probably facilitating the reactivation of either the first set or both sets. On the other hand, in the delayed condition, participants poorly identified the correct location of the first set of objects. In this case, when the two sets were likely encoded as distinct memories, TMR may have induced the reactivation of the second set only (the more recent and the one associated with the auditory cue), therefore creating interference and inducing forgetting of the first set of information.

Overall, these studies showed that i) memory consolidation can be enhanced using acoustic sensory cues; ii) acoustic stimulation modulates hippocampal activity and connectivity during sleep; iii) applying TMR to individual items is feasible. However, they also showed the beneficial TMR effect for visuo-spatial memories seems to be less reliable compared to olfactory stimulation, and that the initial level of memory encoding influences the subsequent TMR effect.

Verbal memories, language learning, and statistical regularities

Some studies have tested the effect of TMR on verbal declarative memories, language learning, and statistical regularities. For example, Cairney and colleagues⁵⁰ tested the effect of TMR on paired word-sound associations. Specifically, they asked participants to learn the association between a written word and a semantically-unrelated spoken word or non-verbal sound. Written words that were cued during NREM sleep, either with a verbal or non-verbal auditory stimulus, were forgotten to a lower degree, indicating a TMR benefit regardless of the verbal/non-verbal nature of the cue. Fuentemilla et al.,⁵¹ used a similar word-sound association task in patients with unilateral and bilateral hippocampal sclerosis. They observed that TMR during SWS reduced forgetting in both unilateral scleroses and in a group of healthy controls, but not in the patients with bilateral sclerosis. Interestingly, they also observed that the volume of the hippocampus, as well as the density of sleep spindles during SWS, was associated with the level of TMR benefit (i.e., performance for the cued items vs uncued item). Groch et al.⁵² asked participants to learn the association between objects visually-presented (20 familiar objects and 20 novel objects) and pseudo-words (e.g. “Wiemel”) acoustically-presented and then to perform an immediate test in which each object was presented again in the screen and the participants had to recall the associated word. During the subsequent NREM sleep, half of the words were played and the next morning participants were tested again on the same task. They observed that TMR facilitated the recall of the words associated with familiar objects, but not for the novel objects. Moreover, they observed an increase theta and spindles activity during sleep after the cue presentation for the items that would be remembered later compared to the stimuli that would be forgotten. This difference was observed only for the familiar items. The authors suggested that TMR may only benefit information that is related to prior knowledges.

Schreiner & Rasch⁵³ applied TMR in the context of language learning. They asked German-speaking participants to learn acoustically-presented Dutch words, which were paired with their written German translation at the center of a screen. During post-learning NREM, half of the Dutch words were replayed (cued words). At the post-sleep test, participants were able to remember the translation of a higher number of cued Dutch words compared to words not replayed during sleep. Also, this improvement was greater than sleeping with no stimulation at all or staying awake. In a subsequent study,⁵⁴ they modified this paradigm including a condition in which the Dutch words were acoustically-presented during sleep, immediately followed by their German translation. In this case, the TMR benefit disappeared. However, when the German translation was presented 1.5s after the Dutch word, the authors again observed the beneficial effect of TMR. The authors suggested that the processing of a cue-induced information occurs during a sensitive plasticity temporal window which can be disrupted by incoming sensory information. Remarkably, these behavioral results replicated their previous findings (improvement of ~10% of correctly remembered words compared to sleep alone or with an unrelated cue),⁵³ strengthening the idea that language learning may indeed be boosted by TMR. They also observed increased theta (4-7 Hz) power and spindle activity following the cue for words that, at the post-test, participants would subsequently remember.⁵⁵ In other words, the greater the theta and spindle oscillatory response to cues during sleep, the higher the probability of correctly remembering that word during subsequent wakefulness. This effect was most evident when comparing memory “gains” (i.e., the word translations that were not remembered during the pre-sleep test but were correctly identified in the post-sleep test) with memory “losses” (i.e., word translations correctly identified pre-sleep but not afterwards), suggesting that increased theta and spindle activity may represent a biomarker of these behavioral changes.

These results indicate that language learning can be facilitated by replaying the to-be-remembered words during sleep, with the caveat that the timing of the acoustic stimulation is critical in this process. Specifically, a second cue may block the ongoing reactivation process elicited by the first cue if the two cues are too close in time (e.g., less than 1.5s). The latter finding was also reported by Farthouat et al.,⁵⁶ who asked participants to learn a list of word-pairs presented at the same time both visually and acoustically. During subsequent SWS, half of the words were presented acoustically, followed by the second word of the pair (or a new one) after 1000-1500ms. Although no benefit of the TMR was shown, they observed increased theta and spindle activity following the first word, while the second word evoked increased theta, while suppressing spindle activity. Similar to Schreiner and colleagues⁵⁵, the authors suggested that a silent period after cue stimulation is needed to allow the memory reactivation process to unfold.

Learning a new language not only requires acquiring the semantic meaning of a written/spoken word, but also learning the grammatical rules underlying that language. In this context, studies have examined whether TMR may facilitate the consolidation of new grammar rules. For instance, Batternik and Paller⁵⁷ tested whether TMR may facilitate rule abstraction and generalization in a language learning task. Participants learned to create phrases by selecting words from an artificial language characterized by five grammatical rules. Every time they selected the correct word, an audio-clip of the word was played (cue), whereas an error signal was presented when an incorrect word was chosen. After the learning phase, participants were tested on the same task with a set of novel words, and this time no feedback was provided. During the following sleep periods, either the learning-specific cues or other auditory words associated with a control task were replayed. At the post-test, participants exposed to the cues showed an increased ability to generalize the grammatical rules to novel words. In a subsequent study,⁵⁸ they asked a group of participants to learn the association between the picture of an object (e.g., an apple) and an artificial word (e.g., “dreep”) visually-presented, while a specific environmental sound (e.g., “crunch” noise) was played for each association. Then participants were asked to perform a speeded recall task, in which the sound associated with a picture was presented while the corresponding artificial word started to appear on the screen (one letter appeared every 2s). Participants pressed a button as soon as they recognized the artificial word, and then typed the word and received visual feedback about their accuracy. The

second group of participants performed a similar task, but in this case, the association was only created between an artificial word presented acoustically and an object (no specific environmental sound was played). During a subsequent nap, half of the environmental sounds/spoken artificial words were replayed during SWS. At the post-sleep test, they observed a TMR benefit (i.e., increased accuracy for cued compared to uncued words) as a function of the amount of REM sleep; only participants with more than 10 minutes of REM sleep showed the TMR benefit, whereas participants with less than 10 minutes of REM showed the opposite effect (i.e., higher accuracy for the uncued compared to the cued associations). No effects on reaction times were observed. A similar result was reported by Tamminen and colleagues,⁵⁹ who failed to show an effect of TMR on a lexical competition task, which tests the level of integration between novel words and pre-existing mental lexicon, but observed that the change in lexical competition for cued items was associated with time spent in REM sleep.

Donohue and Spencer⁶⁰ investigated the effect of using a constant background sounds (instead of specific cues) in the consolidation of verbal information. Specifically, they asked participants to learn a list of semantically-unrelated word pairs while an “ocean” sound was continuously presented throughout the encoding session. After encoding, an immediate cued recall test was performed, during which a single word was presented and the participants had to type the associated word. During subsequent nighttime sleep, participants were continuously exposed to the “ocean” sound, and the next morning they performed a delayed memory test identical to the immediate test. They observed no benefit of the acoustic stimulation compared to sleeping with no sounds. The lack of cueing-effect of this study can be explained by taking into account the procedure used. Different from the other auditory TMR studies, here the sounds were constantly played during the learning phase and were not time-locked to the stimuli onset. This may have caused a non-specific or a weak association between the sound and the word-pairs. Also, a habituation effect may have occurred due to the constant exposure to the sound during wake which may have blocked any potential benefit of re-exposure during sleep (where the sounds were also constantly played).

Hennies and colleagues⁶¹ investigated the effect of TMR on the extraction of statistical regularities, a hallmark of semantic memory.⁶² They created several streams of either auditory stimuli (18 tones) or visual stimuli (a yellow circle moving in 18 different spatial locations). Some of these streams followed a probabilistic sequence whereas the others followed a random structure. After a learning phase in which participants were exposed to the streams, they performed an immediate test in which they had to decide whether each sequence was similar to a stream presented in the learning phase. When tested again after a full night of sleep, participants whose tone sequences were replayed during SWS showed worse performance for both auditory and visual streams compared to participants who had no acoustic stimulation during sleep. The authors suggested that TMR during SWS may have interfered with the ongoing process of abstraction of statistical regularities.

Overall these studies indicate that i) TMR can facilitate the consolidation of visual information but only if the sensory cue is matched with a specific item; ii) TMR induces a cue-evoked increase in theta and spindle activity during sleep; iii) a silent period of at least 1.5s after the sensory stimulation is required to allow an optimal memory reactivation process. At the same time, they showed contrasting results of TMR on language learning and on the extraction of statistical regularities, suggesting that for these memories that require not only the consolidation of the information per se, but also the strengthening of associated memories (e.g., semantic meaning and expectations), the mere reactivation of the encoded information during NREM sleep may not be enough to promote a beneficial learning improvement. Indeed, this learning may require a coordination between NREM and REM sleep, where the integration and reorganization of associated symbols, sounds, and meanings may occur. These results are also consistent with the idea of a complementary role of NREM and REM in integrating associative information in pre-existing neural networks.²⁰

TMR and procedural memories

Although most TMR studies have employed declarative memory tasks, a few studies have investigated the generalizability of this paradigm to procedural tasks. Rasch and colleagues¹¹ asked participants to perform a motor sequence learning (MSL) task, in which participants tapped a sequence (e.g., 4-2-3-1-4) on a keyboard with their non-dominant hand, as fast and accurately as possible. During the task training phase, the scent of a rose was presented. The MSL is considered an *explicit motor task*, which combines procedural and declarative aspects⁶³⁻⁶⁵ and involves the activation of both the cortico-striatal network and the hippocampus.⁶⁶ However, re-exposing the participants to the rose odor during either SWS or REM sleep did not provide any benefit. Laventure et al.⁶⁷ used a similar paradigm, but targeted either N2 sleep or REM sleep for reactivation. Indeed, as expected by the authors, presenting the cue during N2 enhanced motor performance in the post-sleep test compared to odor presentation during REM sleep or presenting an unrelated odor. Moreover, the cue stimulation modified spindle features (i.e., frequency and amplitude), and these changes mediated the observed performance improvement. This result may appear in disagreement with Rasch et al.¹¹. However, Laventure et al.⁶⁷ presented the olfactory stimulus during N2, a stage often associated with motor memory consolidation^{68,69}, whereas Rasch and colleagues used olfactory stimulation during SWS. Also, Rasch et al. noted that the same olfactory stimulus (the scent of a rose) was used to cue both the spatial memory task and the MSL, possibly creating interference in the memory processing of the two tasks. Interestingly, both these studies showed no performance benefit when the TMR was delivered during REM sleep.

Pereira and colleagues⁷⁰ used another sensory modality – touch – to try to improve MSL performance with stimulation during sleep. They developed a system that lightly stimulated participants' fingers during sleep, in a manner that either resembled the learned motor sequence or a different one. Contrary to the authors' initial hypothesis, the stimulation did not produce any performance improvement or impairment, however, they did observe both an increased SO density and a reduction of spindle activity. These results suggest that the sleeping brain may be sensitive to light tactile information, and the constant stimulation can modulate the ongoing brain activity by uncoupling SO-related spindle activity.

In an original study combining TMR with melody production, Antony and colleagues³⁰ developed a task in which participants had to learn to two melodies. Each melody was composed of a sequence of 12-tones, which were also visually represented on a screen by moving dots. Similar to the *Guitar Hero* video game, when a dot reached one of four open circles at the top of the screen, the participant was to tap the corresponding key button, which produced a note of the melody. Tapping the 12-item sequence at the right time resulted in a specific melody. During subsequent NREM sleep, one of the two melodies was acoustically-presented to the participant. At the post-sleep test, participants were more accurate in reproducing the sequence whose melody was presented during sleep compared to the non-replayed melody. Moreover, the difference in performance between cued and uncued sequences was associated with both the amount of SWS and with the number of spindles observed during SWS.

Another set of studies combined TMR with different versions of the serial reaction time task (SRTT). For example, Schonauer et al.⁷¹ presented 4 empty circles at the center of the screen and, during each trial, the circles were filled one at the time to produce a 12-item sequence. Participants were instructed to press the corresponding key button as fast as they could. Each correct response was associated with a specific acoustic cue (a piano tone). During the subsequent sleep, half of the 12-tone were presented for 2 consecutive hours at a pace of 1-s per tone. At the post-test, participants showed a lower number of errors for the cued part of the sequence compared to the uncued part. In another study, visual cues (i.e., faces and objects) could appear in one of 4 spatial locations on the screen,⁷² and participants were to press the corresponding key as fast as possible. As in Schonauer et al.,⁷¹ each key press was associated with a specific tone. The cues were grouped into 2 different 12-item sequences. During NREM sleep, the tones of one of the two sequences were presented again. At post-test, participants were faster and more accurate in performing the cued sequence compared to the uncued one. Moreover, cueing during SWS was associated with increased activity in the bilateral

caudate nuclei and hippocampi at post-test, suggesting an effect of cueing on hippocampal activity.⁷³ Another study employed a similar SRTT task with a 12-element sequence,⁷⁴ but this time an odor was presented every 5 key responses. Participants performed several trials, some of them with random sequences and some with a “fixed” sequences. After a training session, participants were retested immediately and the next morning after a night of sleep. During sleep, half of the participants received the same odor presented in the task during the first 3 hours of SWS, whereas the other half received an odorless vehicle. At the post-sleep test, no effect of TMR on the SRTT was observed. However, participants who were exposed to the odor during SWS performed better in an explicit sequence knowledge test (i.e., a free recall of the sequences) than the participants who received the vehicle, but this effect was significant only for male participants. The authors speculated that sex hormones may have modulated the effect of TMR in female participants.

Recently, Johnson and colleagues⁷⁵ investigated whether TMR could be used to enhance sensorimotor skills. Participants threw a ball aimed at the center of a projected target image located 3 meters in front of them. Five target locations were presented in the task, and each location was associated with a specific auditory cue. Participants who were exposed to the cues during the first 2 cycles of SWS showed better performance at the beginning of the post-sleep test (but not later in the test session) compared to individuals who did not receive any stimulation or remained awake (either undergoing acoustic stimulation or not). This result suggests that TMR may potentially be applied to more complex (in comparison to finger tapping) motor skills, and the authors proposed that TMR might even be used as a tool in physical rehabilitation programs.

Overall these results show a general benefit of TMR on procedural memory, with a stronger effect for memories that have an explicit component and likely require a certain degree of hippocampal involvement. However, further research is required to better understand the efficacy of this technique with more complex procedural and motor knowledge.

TMR and emotional memory

Emotional memories, as defined by Kensinger,⁷⁶ are “*memory of experiences that evoked an emotional reaction*”. Several studies suggest that sleep may facilitate the consolidation of the content as well as modulate the emotional component of these memories.⁷⁷⁻⁷⁹ Based on these findings, a few studies have investigated the effect of TMR on emotional memory. Cairney and colleagues⁸⁰ asked participants to memorize the content and the spatial location (on the screen) of 36 unpleasant and 36 neutral pictures. Each picture was presented with a concurrent semantically-related sound. After a training session, the pictures were presented at the center of the screen, and participants were asked to recall each picture’s previous location. During a subsequent nap period, 36 sounds (18 unpleasant and 18 neutral) were presented once during SWS sleep. At the post-nap test, participants did not show any benefit of TMR for memory accuracy or reaction times. Nevertheless, they observed a negative association between time spent in SWS and the reaction times to the cued unpleasant pictures. In other words, the more time a participant spent in SWS, the faster his/her response to the cued unpleasant pictures.

Sterpenich and colleagues⁸¹ used 90 pictures of unpleasant (e.g., a crying child, an angry face) and 90 pictures of neutral faces, which were presented on the screen paired with a category-specific sound (i.e., a sound for unpleasant and a different sound for neutral pictures). At the end of each picture presentation, participants rated the level of arousal and of pleasantness/unpleasantness experienced from viewing each stimulus. Then auditory cues were played either during N2 or REM sleep. Two control groups did not receive any acoustic stimulation during sleep. At the post-sleep test, participants who were exposed to the cues during REM correctly recognized a greater number of pictures (which were intermixed with 60 new pictures) compared to the other conditions. Moreover, unpleasant faces were remembered better than neutral ones. Interestingly, stimulation during REM sleep was associated with increased activity in the inferior occipital gyrus and in the middle temporal gyrus during the post-sleep test, suggesting that TMR during REM may have strengthened the association between visual and auditory components of each item. This beneficial

effect of stimulating during REM was not confirmed by Lehman and colleagues.⁸² They used a different emotional memory task, in which participant had to memorize a series of word-picture pairs. In an initial learning phase, unpleasant or neutral pictures were paired with auditory neutral words, and half of these words were presented again during NREM or REM sleep. At the post-sleep test, participants exposed to the auditory cues during NREM showed higher recognition for the emotional pictures compared to the neutral pictures. They did not observe any differences in the memory performance for emotional and neutral pictures in participants who were stimulated during REM sleep or wakefulness. Interestingly, the cues during NREM sleep increased both theta and spindle activity, with a greater magnitude increase for cues related to unpleasant stimuli, and these increases were positively associated with post-sleep performance. These results suggest that NREM, rather than REM sleep, may be the optimal stage for the strengthening of emotional memories. However, Ashton and colleagues⁸³ reported no effect of TMR on emotional memories. They tested the recognition of emotional and neutral pictures that were associated with unique sounds. Half of these cues were presented during SWS, but the authors did not observe any benefit of cueing at the post-sleep test compared to sleeping with no cue. However, recognition performance was at ceiling, and the authors suggested that recognition tests may be not sensitive enough to detect TMR benefits. This study prompts a methodological question that future studies need to address: Are recognition tests suitable to study TMR? And to what extent can results from recognition and recall paradigm can be compared?

Using a different paradigm, Groch et al.⁸⁴ investigated whether TMR could modify the interpretation of ambiguous pictures. They used a picture-word association task, in which participants (both adults and adolescents) were exposed to ambiguous scenes (e.g., a band playing in front of an audience) paired with an acoustically-presented word that provided either a positive (“applause”) or a negative (“jeer”) interpretation of the scene. During a learning phase, participants had to visualize the scene and imagine themselves in that situation. In an immediate test session, they were presented the scene and asked to remember the associated word. The next morning, after a night of sleep during which half of the words were presented during SWS, the authors assessed both the memory accuracy and the direction of generalization of this disambiguating process. Specifically, they used a generalization task in which a new set of ambiguous pictures, which had similar content to the pictures seen in the learning phase, were presented to the participants followed by two words that provided either a positive or a negative interpretation of the scene. Participants had to rate how well each word fit the scene. They observed that both adults and adolescents had better memory for words cued during SWS. They also showed that cueing positive words during sleep led to an increase “fit” of the novel positive words to the novel scenes presented in the generalization task. The authors suggested that TMR can bias the interpretation of the ambiguous situation and that TMR may be used to as a tool to modulate emotional processing in such situations.

Another set of studies combined TMR with a fear conditioning paradigm. Hauner and colleagues⁸⁵ presented a series of faces (conditioned stimuli, CS+) paired with a mild electric shock (unconditioned stimulus, US) to participants while they were also exposed to a background odor. They used two olfactory stimuli during the conditioning phase, and then re-exposed the participants to one of the two odors during subsequent SWS. This procedure enhanced the fear extinction (i.e., the reduction of fear response, here quantified by the reduced skin conductance response, SCR) only for the stimuli associated with the odor presented during SWS, indicating a physiological consequence of TMR and a specificity of the stimulation. Moreover, participants showed reduced activity in the hippocampus, anterior cingulate cortex, and insula when re-exposed to the CS+ in wakefulness. Similar findings were reported by He and colleagues,⁸⁶ who used an analogous paradigm, in which an auditory tone (CS+) was associated with a mild electrical shock, and a second tone was never presented with the shock (CS-). The association between the tone and the electrical shock during wakefulness enhanced fear responses (as indexed by increased SCR). Then, CS+ was continuously presented during SWS. When re-exposed to the CS+ during subsequent wakefulness,

participants showed a reduced fear response (i.e., increased fear extinction) compared to subjects who received the CS- or no auditory cue during sleep.

Different from the previous studies, Rihm and Rasch⁸⁷ used a sensory stimulus as the US. Specifically, during a conditioning phase, eight neutral tones were presented, and after each tone, the participants were asked whether they would expect an odor or not. After the expectancy rating, four tones were matched with an unpleasant odor (CS+) and four with an odorless vehicle (CS-). At the beginning and at the end of the session participants rated the level of arousal and valence elicited by each sound. During either subsequent N2 or REM sleep, participants were re-exposed to half of the sounds (2 CS+ and 2 CS- associated sounds). Two days later, participants performed a second experimental session with the same task, but this time no odor was delivered after the sound presentation. Contrary to their initial hypothesis, no specific effect of TMR during REM sleep was observed. However, at the second session, participants showed a reduction in their subjective arousal ratings for the sounds presented during sleep compared to the sounds who associated CS+ and CS- vehicle were not presented during sleep. Ai and colleagues⁸⁸ further investigated the role of TMR with fear conditioning paradigms, but focused on fear reinstatement rather than extinction. They paired one of two colored squares with a mild shock (CS+) whereas the other colored square was never paired with the shock (CS-). Twenty-four hours later, participants underwent an extinction session, in which the two squares were presented again paired with auditory cues, but this time the stimuli were never associated with an electrical shock. The extinction procedure was successful, and the participants showed a reduced fear response compared to the conditioning session. The auditory cues were then presented during SWS or during a period of wakefulness. The authors observed that participants who were re-exposed to the cues during sleep showed a reinstated fear response, while those re-exposed to the cues during wakefulness maintained the fear extinction.

With the exception of the Rihm and Rasch⁸⁷ results (who, differently from the other studies, targeted N2 or REM sleep), these findings indicate that fear memories may be altered during SWS using a TMR-like paradigm. Based on these results, it has been proposed that re-targeting emotional memories during sleep could facilitate the treatment of disorders characterized by emotional dysregulation, such as phobias or mood disorders.^{32, 89} This idea was tested in another study by Rihm and colleagues⁹⁰, who applied the TMR paradigm to a group of patients with spider phobia. Patients underwent an exposure therapy, and if they reported that the session was successful, they were exposed to an odor at the end of the session. Before and after the therapy session, pictures of spiders and moths were presented to the patients, and they were asked to rate their subjective level of arousal while viewing these stimuli, the fear elicited by these pictures, and how close they would be able to approach them. During a subsequent afternoon nap, the odor or an odorless vehicle was presented during NREM sleep. Another group of patients remained awake after the exposure therapy. A week later, patients underwent a second therapy session. Authors observed an improvement in all the subjective and physiological (i.e., SCR) outcomes, regardless of the odor re-exposure, suggesting that TMR may not facilitate positive clinical outcomes compared to the simple passage of time. Also, Groch et al.⁹¹ tested the effect of TMR on modifying the interpretation of ambiguous pictures in children and adolescents with social anxiety disorders (SAD), who usually show a bias toward negative interpretation of events. They employed the same paradigm used in their previous study with healthy adolescents (see above Ref. ⁸⁴). Both SAD and healthy controls showed a memory benefit for the cued scenes, regardless of their valence. This effect disappeared one week later when participants were tested again with the same task. However, the authors observed that one-week later SAD rated the negative ambiguous scenes as less pleasant and less arousing. Thus, TMR may be able to modulate the emotional tone of memories, which decreased after a week from the first exposure to these events.

Overall, these studies show mixed results for the effect of TMR on emotional memories. Also, whether NREM or REM sleep is the optimal stage for cueing emotional memories remains unclear. Finally, even if TMR applied to fear conditioning memory seems to be successful in reducing fear responses or reinstate it, depending on the paradigm, see Ref. ⁸⁸, the translation of this paradigm to a clinical context did not yield positive, long-term outcomes. Therefore, while TMR may have the

potential to be used as a tool to address psychiatric issues, further research is needed to define the right setting to promote positive clinical outcomes.

Application of TMR in other contexts

In this section, we will review studies that have diverged from standard memory tasks and investigated the potential of TMR in different contexts, such as creativity, social bias, and body perception.

Creativity

Sleep has been shown to promote the formation of associative memories, and these processes seem to rely on both NREM and REM sleep.^{20, 92} In this context, Ritter, and colleagues⁹³ explored whether TMR could enhance creativity-related processes during sleep. They employed the Unusual Uses Task,⁹⁴ in which participants have to list some solutions for a given problem, and then select the idea they think is the most creative. While they were performing the task, participants were exposed to one odor (either orange or vanilla), which was then presented again during the whole night of sleep in one group, whereas a second group was exposed to an unassociated odor, and a third group was not exposed to any scent. At the post-sleep test, participants exposed to the cue odor provided a higher number of solutions for the problems and correctly selected the most creative solution. Although the authors suggested that TMR can indeed boost creativity, possibly enhancing the consolidation and reorganization of associative memories, the lack of polysomnographic recording limits inferences about the mechanisms underlying this creativity effect.

Social bias

Hu and colleagues³¹ recently tested whether TMR could modify implicit social biases. They used two versions of the implicit association test, a task widely used to assess the automatic associations between mental representations of social groups and their attributes. Using this task, they tested the strength of the association between female/male faces with art or science words (gender bias), and the association of Black/White faces with positive and negative words (race bias). As expected, in a baseline test, female faces were associated with art words more than with science words, and Black faces were associated with negative words more than positive words. After this baseline, participants were trained to respond only to the counter-bias associations (e.g., female face with a science word), and each time a counter-bias association was presented, a sound was delivered via speakers (one sound for the gender trials and one sound for race trials). During a subsequent daytime nap, one of the two sounds was presented during SWS. At the post-nap test, participants showed a reduced implicit bias for the cued associations compared to the uncued ones, and this effect was still present 7-days later. Moreover, this effect was positively associated with the combination of time spent in SWS and REM sleep, suggesting that these two sleep stages interact to modify social bias by integrating the reactivated information (i.e., the counter-bias association) into pre-existing associative knowledge networks (similarly to what was observed for associative memories, see Ref. 20).

Body-perception

Honma and colleagues⁹⁵ tested the effect of TMR on the rubber-hand illusion. In this illusion, a participant sees an artificial hand next to his/her body while his/her own hand is covered. When a tactile stimulation is applied to the participant's hand synchronously with a stimulation on the artificial hand, the participant begins to perceive the artificial hand as his/her own. In their study, the researchers presented an auditory cue while creating the rubber-hand illusion (i.e., while the participant and the artificial hands were concurrently stimulated with small paintbrushes). During the following two nights, participants were exposed either to the task-specific cue, a new auditory stimulus, or slept without any stimulation. The authors observed that the cue stimulation increased

both the feeling of body ownership (i.e., the feeling that the artificial hand was their real hand) and the proprioceptive drift (i.e., the perception of the location of the artificial hand). In other words, TMR was able to modulate individuals' body perception, inducing a visuo-proprioceptive recalibration. The authors proposed that TMR may have strengthened the connectivity between the hippocampus and posterior parietal cortex, an area associated with multisensory integration.⁹⁶ However, it should be noted that in this study sleep was assessed through an automated wireless system that classifies sleep stages based on the signal recorded on the forehead via dry electrodes.⁹⁷ This system has several limitations, including poor REM classification and the impossibility to extract sleep features, such as SO and sleep spindles.⁹⁸ The constraints of this system limits inferences that can be made about TMR-induced neurological activity favoring the integration of visuo-proprioceptive information.

Differences between sensory cues

Besides one study using tactile stimulation,⁷⁰ studies with TMR have capitalized either on olfactory or auditory cues (see Table 1). The choice between different sensory stimuli affects both the procedure used and the behavioral (and physiological) outcomes obtained. Indeed, studies using olfactory stimuli have consistently produced a beneficial effect for declarative and emotional memories (with the exception of fear conditioning), but not for procedural memories. Importantly, these benefits have been achieved without any negative impact on sleep architecture. These studies suggest that odors may directly bias hippocampal activity, facilitating the processing of hippocampal-dependent information. Therefore, olfactory stimuli may be the optimal choice for improving declarative information. However, the use of several odorants at the same time, to target only specific items, may be complicated due to the risk of olfactory fatigue. Indeed, no study has used odors to target individual items, only large sets of stimuli. Also, odor stimulation does not allow for clear temporal precision in stimulus delivery, thereby making its use with other techniques, such as closed-loop stimulation (see below), complicated. Auditory cues may be optimal stimuli for systems that require a precise delivery time. In addition, several different cues can be used in the same experiment, and also allows for cues to be semantically-related to individual items. However, whether there is an advantage of using cues conceptually associated with the learned material is still debated⁹⁹ and requires further exploration. Additionally, auditory stimuli can be used with less invasive instrumentation (e.g., earphones or speaker) compared to odors, which require the use of olfactometers and nasal masks (or similar delivery systems). Auditory stimuli can also potentially be used to create wearable systems for TMR stimulation, even using smartphones or analogous devices. However, although TMR with auditory cues has been shown to improve visuospatial learning, language learning, procedural skills and fear conditioning, these stimuli have produced less reliable, and sometimes contrasting, results. Also, acoustic cues can produce transient arousals, wake up participants, or even be delivered under the auditory perceptual threshold and ultimately not processed by the sleeping brain. Therefore, it is important to take particular care when setting the volume of these cues. For example, the procedure may include measuring individual's acoustic threshold level during a pre-sleep wakefulness, or using adaptive procedure to adjust the volume if arousals are detected or if no spindles or SO are evoked.

Neural correlates of TMR

TMR has been shown to modify brain activity during sleep. For example, fMRI studies testing declarative memories have observed increased activation of the anterior and posterior hippocampus,¹¹ as well as activation of the left hippocampus during olfactory stimulation, in SWS.³³ Acoustic stimulation during SWS has been associated with increased activity in the parahippocampal cortex, and with a greater functional connectivity of this region with the occipital cortex.^{27, 41} Greater activation of the occipital cortex was also observed during stimulation in REM sleep.⁸¹ At the electrophysiological level, auditory cues have been associated with increased delta activity,^{42, 44}

which is consistent with previous studies showing that the presentation of sounds or tones during NREM sleep enhances SWA (see Ref. ¹⁰⁰). Also, both olfactory³⁸ and acoustic stimulation^{42, 51, 53, 56} produce an increase in theta and spindle activity, suggesting that TMR may promote memory consolidation by modulating these oscillatory patterns. According to Schreiner and Rasch¹⁰¹, the observed theta activity may represent the reactivation of a memory, which is then consolidated by the following spindles. However, if a paradigm involves the presentation of several consecutive cues during sleep, the timing of the following cue is critical, as it has been shown that cues presented 1500ms after the first one can impair memory consolidation.^{54, 56} Therefore, the timing of the cue delivery may be a key factor to promote memory reactivation. To test this possibility, Batterink and colleagues,⁵⁸ re-analyzed previous data from Rudoy et al.⁴⁰ and Creery et al.⁴² to investigate whether TMR stimulation has a different effect as a function of the phase of the SO in which the cue is delivered. They found that delivering the cue in a phase bin between 180° to 270° degrees produced the most beneficial effect (see Fig.2a for the relationship between phases and SO states). In other words, the items associated with the cues presented in that phase were the ones remembered better.

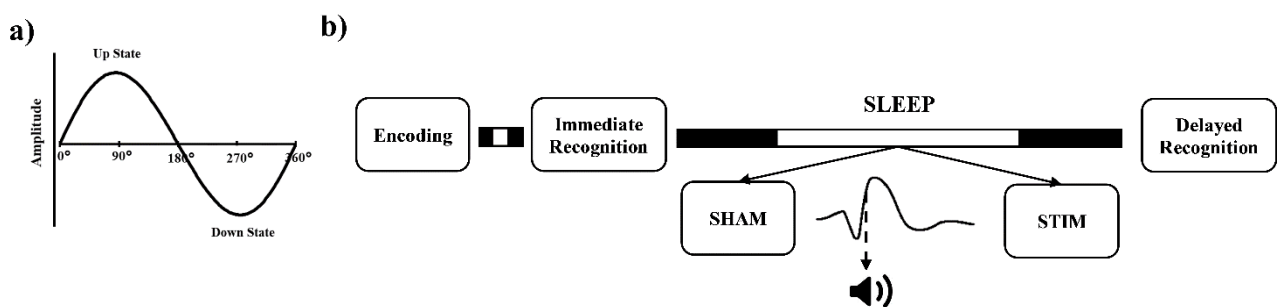


Figure 2. Schematic representation of the auditory closed-loop stimulation (ASCL) method. a) Slow oscillation (SO) up- and down-state and corresponding angular phase. **b)** Schema of an ASCL paradigm. Participants perform an immediate memory test after encoding some to-be-remembered material. During the subsequent sleep period, an acoustic cue is presented during the up-state of the slow oscillation (STIM) or no cue is presented (SHAM). After the sleep period, participants perform a delayed memory test. Performance is often computed as the change between the immediate and the delayed test as a function of the condition (STIM or SHAM).

Taken together, these findings suggest that sensory stimulation during sleep can affect the ongoing oscillatory events underlying memory process, which may promote systemic changes in both memory and sensory regions.

Looking forward: Combining TMR with other stimulation techniques

New approaches have turned out to be successful in inducing sleep-related memory enhancement with minimum invasiveness. Ngo and colleagues¹⁰² developed an auditory closed-loop feedback system (ACLS), based on an adaptive amplitude threshold method, to detect online SO activity in order to send a brief auditory stimulation (i.e., 50-ms bursts of pink noise) during the SO up-state (Fig.2). With this method, they were able to increase SO power, boost phase-locked spindle activity during the SO up-state, and enhance memory performance in a word-paired associates task compared to a control condition. These results were replicated in a subsequent study by the same group¹⁰³ and by other research groups using different ACLS.¹⁰⁴⁻¹⁰⁶ Altogether, these studies systematically indicate that the coupling between SO and spindles (in particular fast spindles, 12-15Hz) may be a key mechanism in promoting memory consolidation during sleep, and this mechanism can be boosted by delivering an acoustic stimulus in a specific phase of the SO (i.e., the up-phase). More recently, Shimizu and colleagues¹⁰⁷ developed a system that integrates ACLS and

TMR techniques. Specifically, the system was able to detect ongoing EEG activity and deliver specific cues, which were associated with specific information during wakefulness, during the up-state of the SO. They showed that this stimulation improves navigation skills compared to subjects who slept with no stimulation after the learning session, and similar to previous studies, the acoustic stimulation increased spindles activity locked to the up-state of the SO. While this study was the first attempt to combine ACSL with TMR, the authors could not disentangle whether the observed beneficial effects were the consequence of the specific auditory cue or of the cue-SO phase-locking.

Interestingly, recent studies used rhythmic acoustic sequences to enhance different sleep oscillations. Antony and Paller¹⁰⁸ delivered oscillating sounds (white noise) at slow and fast spindles frequency (12Hz and 15Hz, respectively) during N2 and SWS in a 2s-on 8s-off sequence. The stimulation induced a frequency-specific modulation of parietal spindles (i.e., increased slow spindles in response to 12Hz stimulation and fast spindles as a consequence of 15Hz sounds). Similarly, Lustenberger and colleagues¹⁰⁹ delivered sounds either at 14Hz or 40Hz (1s-on, 3s-off) throughout a daytime nap. Both sounds produced increased spindle activity compared to a sham stimulation.

Overall these results indicate that memory-related sleep oscillations can be modulated via acoustic stimulation either in a closed-loop or rhythmic fashion. A further step in this line of research would be combining ACLS/auditory rhythmic stimulation with TMR, thus enhancing sleep oscillations which are purported to drive reactivation, while specifying which contents need to be reactivated first. In this case, researchers should test whether the use of TMR in combination with these systems may be more effective (in terms of memory improvement) than the use of these techniques alone. Also, researchers should pay attention not only to the potential memory improvement of the specific targeted items, but also to whether this “enhancement” leads to an impairment (compared to a control condition) of the uncued information. In other words, is there a cost of targeting specific information? And to what extent can memory be improved via acoustic stimulation?

Conclusion

All in all, the studies presented in this review show that memory consolidation can indeed be shaped by non-invasive sensory stimulation, either using olfactory or auditory stimuli. Information from different memory domains (declarative, procedural, emotional) can be successfully targeted during sleep. Therefore, TMR may hold far-reaching implications for future neuroscientific investigations and for clinical purposes. However, the potential benefit depends on the paradigm used, the type of the cues used, and the timing of the stimulation. Moreover, at the translational level, the application of TMR to address real-world issues, for example increasing learning abilities in students,⁹⁹ to compensate the cognitive deficits observed in sleep¹¹⁰ or neurodegenerative disorders,¹¹¹ to facilitate rehabilitation programs¹¹² or to aid clinicians in treating psychiatric disorders,⁸⁹ has yet to be achieved. To sum up, the studies presented in the current review show promising but not systematic results of TMR, and further studies are needed to optimize this technique and facilitate its translation to real-world applications.

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