

1 **Shaping memory consolidation via targeted memory reactivation**
2 **during sleep**

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1 **Abstract**

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

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1 Introduction

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3 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}

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10 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}

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15 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.

16 17 18 19 20 21 22 23 **Physiological mechanisms of memory consolidation during sleep.**

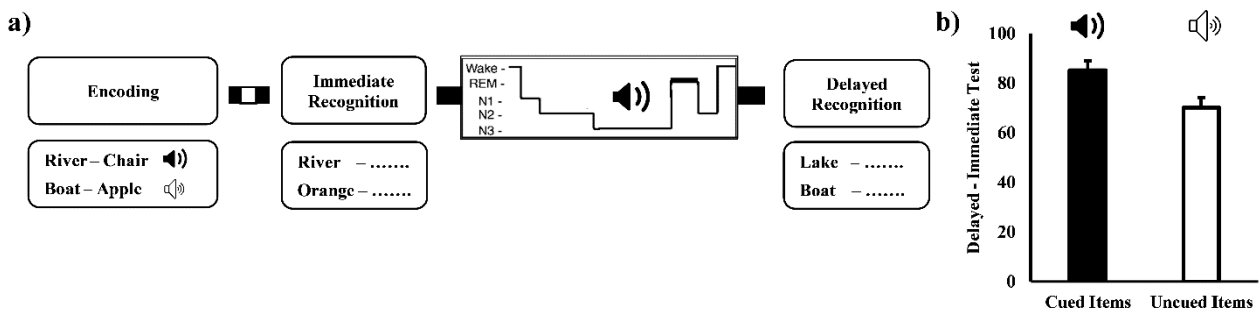
24 According to the *active system consolidation model* (ASC),^{1,7} which is based on the *two-stage model of memory trace formation*,^{4,5} optimal memory consolidation may depend on the temporal coupling of cortical slow oscillations (SO; waves of .5-1Hz and amplitude $\geq 75\mu\text{V}$), thalamic 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

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42 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

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

4 *Playing with Memory During Sleep: The Targeted Memory Reactivation Paradigm*

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 6 Studies in both humans²⁷ and animals²⁸ have shown that reactivation of specific memories
 7 during sleep can be modulated using external stimulation. Specifically, it has been observed that
 8 matching a sensory stimulus (e.g., odor or sound *cue*) with target information (e.g., pairs of words,
 9 objects, motor sequences), and then presenting the *cue* alone during sleep, facilitates the
 10 neurophysiological processes (e.g., coordination of sleep spindles and SO) underpinning memory
 11 consolidation. Thus, presenting learned cues while asleep seems to be able to reactivate related (i.e.,
 12 *cued*) declarative, procedural and emotional material. This paradigm, named *targeted memory*
 13 *reactivation* (TMR), has been successfully used to improve visuospatial¹¹ and verbal memories,²⁹
 14 strengthen motor skills,³⁰ modify implicit social biases³¹ and enhance fear extinction (see Ref. 32;
 15 Fig.1). However, these studies also show that results depend on the type of memory investigated, the
 16 task employed, the sensory cue used, the timing of the cue delivery and the specific sleep stage of
 17 stimulation.
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 20 **Figure 1. Schema of a targeted memory reactivation (TMR) paradigm.** **a)** During the encoding
 21 phase, participants learn some material (e.g., unrelated pair of words). Items are associated with some
 22 sensory cue(s) (e.g., semantically related sound cues). Then, they perform an immediate memory test
 23 (e.g., a cued-recall task) followed by a period of sleep (or wake). During specific sleep stages (i.e.,
 24 N2, N3, REM), one (or more) of the associated cue(s) is presented several times. After the sleep
 25 period, a delayed test is performed. **b)** Example of a typical TMR result. Performance is often
 26 computed as the change between the immediate and the delayed tests as a function of the condition
 27 (Cued vs Uncued items). Cued items (items whose associated cue was presented during sleep)
 28 are remembered better than uncued items (items whose associated cue was not presented during sleep).
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32 Here, we will review the effects of TMR for different memory domains (declarative,
 33 procedural, emotional, see also Table 1), discussing strengths and weaknesses of different protocols
 34 and the efficacy of the various sensory stimulations (olfactory, auditory). We will also discuss other
 35 exciting paradigms that use sensory stimuli via *close-loop stimulation* or *rhythmic auditory sequences*
 36 to shape memory consolidation, and can be combined with TMR protocols.
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1 **Table 1. Main information of targeted-memory reactivation studies presented in this review.**

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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

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

6 *Visuo-Spatial Memory*

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

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

4 Cordi and colleagues³⁵ focused on TMR during REM sleep, and replicated the finding that
5 memory stability is not affected by olfactory TMR during this stage. Specifically, odor and vehicle
6 control stimulation during REM sleep produced the same performance outcome. Moreover,
7 performance outcomes for both these conditions was decreased compared to TMR during SWS,³³
8 suggesting that TMR is beneficial only when performed in SWS. The same group further tested the
9 relationship between TMR and interfering memories.³⁶ Specifically, they asked participants to learn
10 a series object-location pairs while an odor was presented (Day 1). Twenty-four hours later (Day 2),
11 participants were asked to learn a different set of object-location pairs with no odor pairing. During
12 the following sleeping period, either the Day 1 odor or an odorless vehicle was delivered during SWS.
13 After about 40 minutes of SWS they were awakened and tested on the object-location task encoded
14 on Day 2, and then on the object-location task encoded on Day 1. Contrary to the authors' hypothesis,
15 the context odor (associated with Day 1 task) did not impair the consolidation of the Day 2 task, but
16 rather promoted its stabilization (i.e., there was lower “intrusion” from the Day 1 task compared to
17 the vehicle stimulation condition). The authors speculated about this counterintuitive effect,
18 suggesting that perhaps memory of the Day 1 task, encoded 24hrs before, was too weak to be
19 reactivated during Day 2 sleep, or that the context odor could have also been associated with the Day
20 2 task due to the similarity of the two tasks, thereby promoting the stabilization of the Day 2 memories
21 with the Day 1 odor. This idea leads to an interesting hypothesis: olfactory TMR may also promote
22 the stabilization of information semantically or conceptually-related to the cued-memory.

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

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

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

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

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

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

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

29 *Verbal memories, language learning, and statistical regularities*

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

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

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

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

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

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

27 Hennies and colleagues⁶¹ investigated the effect of TMR on the extraction of statistical
28 regularities, a hallmark of semantic memory.⁶² They created several streams of either auditory stimuli
29 (18 tones) or visual stimuli (a yellow circle moving in 18 different spatial locations). Some of these
30 streams followed a probabilistic sequence whereas the others followed a random structure. After a
31 learning phase in which participants were exposed to the streams, they performed an immediate test
32 in which they had to decide whether each sequence was similar to a stream presented in the learning
33 phase. When tested again after a full night of sleep, participants whose tone sequences were replayed
34 during SWS showed worse performance for both auditory and visual streams compared to
35 participants who had no acoustic stimulation during sleep. The authors suggested that TMR during
36 SWS may have interfered with the ongoing process of abstraction of statistical regularities.

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

50

51 **TMR and procedural memories**

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

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

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

39 Another set of studies combined TMR with different versions of the serial reaction time task
40 (SRTT). For example, Schonauer et al.⁷¹ presented 4 empty circles at the center of the screen and,
41 during each trial, the circles were filled one at the time to produce a 12-item sequence. Participants
42 were instructed to press the corresponding key button as fast as they could. Each correct response
43 was associated with a specific acoustic cue (a piano tone). During the subsequent sleep, half of the
44 12-tone were presented for 2 consecutive hours at a pace of 1-s per tone. At the post-test, participants
45 showed a lower number of errors for the cued part of the sequence compared to the uncued part. In
46 another study, visual cues (i.e., faces and objects) could appear in one of 4 spatial locations on the
47 screen,⁷² and participants were to press the corresponding key as fast as possible. As in Schonauer et
48 al.,⁷¹ each key press was associated with a specific tone. The cues were grouped into 2 different 12-
49 item sequences. During NREM sleep, the tones of one of the two sequences were presented again. At
50 post-test, participants were faster and more accurate in performing the cued sequence compared to
51 the uncued one. Moreover, cueing during SWS was associated with increased activity in the bilateral

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

12 Recently, Johnson and colleagues⁷⁵ investigated whether TMR could be used to enhance
13 sensorimotor skills. Participants threw a ball aimed at the center of a projected target image located
14 3 meters in front of them. Five target locations were presented in the task, and each location was
15 associated with a specific auditory cue. Participants who were exposed to the cues during the first 2
16 cycles of SWS showed better performance at the beginning of the post-sleep test (but not later in the
17 test session) compared to individuals who did not receive any stimulation or remained awake (either
18 undergoing acoustic stimulation or not). This result suggests that TMR may potentially be applied to
19 more complex (in comparison to finger tapping) motor skills, and the authors proposed that TMR
20 might even be used as a tool in physical rehabilitation programs.

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

25

26 **TMR and emotional memory**

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

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

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

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

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

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

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

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

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

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

3 4 **Application of TMR in other contexts**

5
6 In this section, we will review studies that have diverged from standard memory tasks and
7 investigated the potential of TMR in different contexts, such as creativity, social bias, and body
8 perception.

9 10 *Creativity*

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

23 24 *Social bias*

25 Hu and colleagues³¹ recently tested whether TMR could modify implicit social biases. They
26 used two versions of the implicit association test, a task widely used to assess the automatic
27 associations between mental representations of social groups and their attributes. Using this task, they
28 tested the strength of the association between female/male faces with art or science words (gender
29 bias), and the association of Black/White faces with positive and negative words (race bias). As
30 expected, in a baseline test, female faces were associated with art words more than with science
31 words, and Black faces were associated with negative words more than positive words. After this
32 baseline, participants were trained to respond only to the counter-bias associations (e.g., female face
33 with a science word), and each time a counter-bias association was presented, a sound was delivered
34 via speakers (one sound for the gender trials and one sound for race trials). During a subsequent
35 daytime nap, one of the two sounds was presented during SWS. At the post-nap test, participants
36 showed a reduced implicit bias for the cued associations compared to the uncued ones, and this effect
37 was still present 7-days later. Moreover, this effect was positively associated with the combination of
38 time spent in SWS and REM sleep, suggesting that these two sleep stages interact to modify social
39 bias by integrating the reactivated information (i.e., the counter-bias association) into pre-existing
40 associative knowledge networks (similarly to what was observed for associative memories, see Ref.
41 20).

42 43 *Body-perception*

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

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

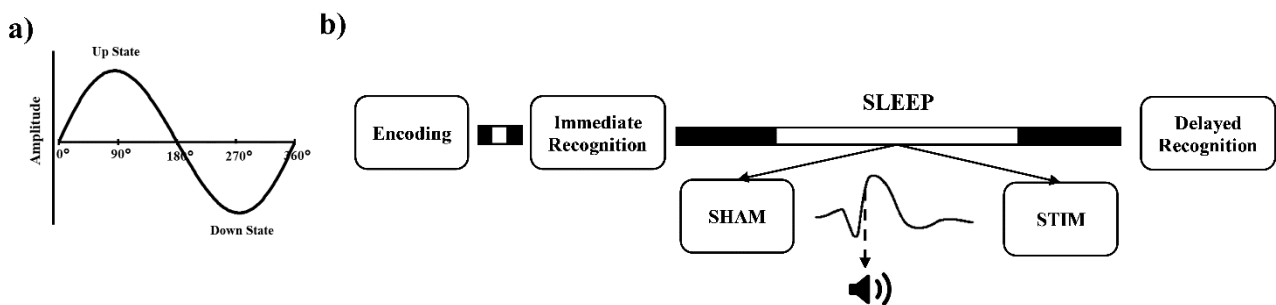
14 **Differences between sensory cues**

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

44 **Neural correlates of TMR**

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

1 which is consistent with previous studies showing that the presentation of sounds or tones during
 2 NREM sleep enhances SWA (see Ref. ¹⁰⁰). Also, both olfactory³⁸ and acoustic stimulation^{42, 51, 53, 56}
 3 produce an increase in theta and spindle activity, suggesting that TMR may promote memory
 4 consolidation by modulating these oscillatory patterns. According to Schreiner and Rasch¹⁰¹, the
 5 observed theta activity may represent the reactivation of a memory, which is then consolidated by the
 6 following spindles. However, if a paradigm involves the presentation of several consecutive cues
 7 during sleep, the timing of the following cue is critical, as it has been shown that cues presented
 8 1500ms after the first one can impair memory consolidation.^{54, 56} Therefore, the timing of the cue
 9 delivery may be a key factor to promote memory reactivation. To test this possibility, Batterink and
 10 colleagues,⁵⁸ re-analyzed previous data from Rudoy et al.⁴⁰ and Creery et al.⁴² to investigate whether
 11 TMR stimulation has a different effect as a function of the phase of the SO in which the cue is
 12 delivered. They found that delivering the cue in a phase bin between 180° to 270° degrees produced
 13 the most beneficial effect (see Fig.2a for the relationship between phases and SO states). In other
 14 words, the items associated with the cues presented in that phase were the ones remembered better.
 15



16
17

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

25

26 Taken together, these findings suggest that sensory stimulation during sleep can affect the
 27 ongoing oscillatory events underlying memory process, which may promote systemic changes in both
 28 memory and sensory regions.
 29

30

30 Looking forward: Combining TMR with other stimulation techniques

31

32 New approaches have turned out to be successful in inducing sleep-related memory
 33 enhancement with minimum invasiveness. Ngo and colleagues¹⁰² developed an auditory closed-loop
 34 feedback system (ACLS), based on an adaptive amplitude threshold method, to detect online SO
 35 activity in order to send a brief auditory stimulation (i.e., 50-ms bursts of pink noise) during the SO
 36 up-state (Fig.2). With this method, they were able to increase SO power, boost phase-locked spindle
 37 activity during the SO up-state, and enhance memory performance in a word-paired associates task
 38 compared to a control condition. These results were replicated in a subsequent study by the same
 39 group¹⁰³ and by other research groups using different ACLS.¹⁰⁴⁻¹⁰⁶ Altogether, these studies
 40 systematically indicate that the coupling between SO and spindles (in particular fast spindles, 12-
 41 15Hz) may be a key mechanism in promoting memory consolidation during sleep, and this
 42 mechanism can be boosted by delivering an acoustic stimulus in a specific phase of the SO (i.e., the
 43 up-phase). More recently, Shimizu and colleagues¹⁰⁷ developed a system that integrates ACLS and

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

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

15 Overall these results indicate that memory-related sleep oscillations can be modulated via
 16 acoustic stimulation either in a closed-loop or rhythmic fashion. A further step in this line of research
 17 would be combining ACSL/auditory rhythmic stimulation with TMR, thus enhancing sleep
 18 oscillations which are purported to drive reactivation, while specifying which contents need to be
 19 reactivated first. In this case, researchers should test whether the use of TMR in combination with
 20 these systems may be more effective (in terms of memory improvement) than the use of these
 21 techniques alone. Also, researchers should pay attention not only to the potential memory
 22 improvement of the specific targeted items, but also to whether this “enhancement” leads to an
 23 impairment (compared to a control condition) of the uncued information. In other words, is there a
 24 cost of targeting specific information? And to what extent can memory be improved via acoustic
 25 stimulation?
 26

27 Conclusion

28 All in all, the studies presented in this review show that memory consolidation can indeed be
 29 shaped by non-invasive sensory stimulation, either using olfactory or auditory stimuli. Information
 30 from different memory domains (declarative, procedural, emotional) can be successfully targeted
 31 during sleep. Therefore, TMR may hold far-reaching implications for future neuroscientific
 32 investigations and for clinical purposes. However, the potential benefit depends on the paradigm used,
 33 the type of the cues used, and the timing of the stimulation. Moreover, at the translational level, the
 34 application of TMR to address real-world issues, for example increasing learning abilities in
 35 students,⁹⁹ to compensate the cognitive deficits observed in sleep¹¹⁰ or neurodegenerative
 36 disorders,¹¹¹ to facilitate rehabilitation programs¹¹² or to aid clinicians in treating psychiatric
 37 disorders,⁸⁹ has yet to be achieved. To sum up, the studies presented in the current review show
 38 promising but not systematic results of TMR, and further studies are needed to optimize this technique
 39 and facilitate its translation to real-word applications.
 40

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 44

45 References

- 46 1. Diekelmann S, Born J. 2010. The memory function of sleep. *Nat Rev Neurosci*; **11**:114-26.
- 47 2. Rasch B, Born J. 2013. About sleep's role in memory. *Physiol Rev*; **93**:681-766.
- 48 3. Tononi G, Cirelli C. 2014. Sleep and the price of plasticity: From synaptic and cellular
 49 homeostasis to memory consolidation and integration. *Neuron*; **81**:12-34.

- 1 4. Buzsáki G. 1989. Two-stage model of memory trace formation: A role for “noisy” brain
2 states. *Neuroscience*; **31**:551-70.
- 3 5. McClelland JL, McNaughton BL, O'Reilly RC. 1995. Why there are complementary
4 learning systems in the hippocampus and neocortex: Insights from the successes and failures of
5 connectionist models of learning and memory. *Psychol Rev*; **102**:419.
- 6 6. Saletin JM, Walker MP. 2012. Nocturnal mnemonics: Sleep and hippocampal memory
7 processing. *Front Neurol*. 2012-May-1; **3**.
- 8 7. Born J, Wilhelm I. 2012. System consolidation of memory during sleep. *Psychol Res*;
9 **76**:192-203.
- 10 8. Wilson MA, McNaughton BL. 1994. Reactivation of hippocampal ensemble memories
11 during sleep. *Science*; **265**:676-9.
- 12 9. Dave AS, Margoliash D. 2000. Song replay during sleep and computational rules for
13 sensorimotor vocal learning. *Science*; **290**:812-6.
- 14 10. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, Phillips C, Degueldre C,
15 Del Fiore G, Aerts J. 2004. Are spatial memories strengthened in the human hippocampus during
16 slow wave sleep? *Neuron*; **44**:535-45.
- 17 11. Rasch B, Büchel C, Gais S, Born J. 2007. Odor cues during slow-wave sleep prompt
18 declarative memory consolidation. *Science*; **315**:1426-9.
- 19 12. Schönauer M, Alizadeh S, Jamalabadi H, Abraham A, Pawlizki A, Gais S. 2017. Decoding
20 material-specific memory reprocessing during sleep in humans. *Nat Commun*; **8**.
- 21 13. Staresina BP, Bergmann TO, Bonnefond M, Van Der Meij R, Jensen O, Deuker L, Elger
22 CE, Axmacher N, Fell J. 2015. Hierarchical nesting of slow oscillations, spindles and ripples in the
23 human hippocampus during sleep. *Nat Neurosci*; **18**:1679–86.
- 24 14. Mak-McCully RA, Rolland M, Sargsyan A, Gonzalez C, Magnin M, Chauvel P, Rey M,
25 Bastuji H, Halgren E. 2017. Coordination of cortical and thalamic activity during non-rem sleep in
26 humans. *Nat Commun*; **8**:15499.
- 27 15. Maingret N, Girardeau G, Todorova R, Goutierre M, Zugaro M. 2016. Hippocampo-cortical
28 coupling mediates memory consolidation during sleep. *Nat Neurosci*; **19**:959-64.
- 29 16. Wei Y, Krishnan GP, Komarov M, Bazhenov M. 2017. Differential roles of sleep spindles
30 and sleep slow oscillations in memory consolidation. *bioRxiv*:153007.
- 31 17. Genzel L, Kroes MC, Dresler M, Battaglia FP. 2014. Light sleep versus slow wave sleep in
32 memory consolidation: A question of global versus local processes? *Trends Neurosci*; **37**:10–9.
- 33 18. Hasselmo ME, McGaughy J. 2004. High acetylcholine levels set circuit dynamics for
34 attention and encoding and low acetylcholine levels set dynamics for consolidation. *Prog Brain*
35 *Res*; **145**:207-31.
- 36 19. Hasselmo ME. 2009. A model of episodic memory: Mental time travel along encoded
37 trajectories using grid cells. *Neurobiol Learn Mem*; **92**:559-73.
- 38 20. Whitehurst LN, Cellini N, McDevitt EA, Duggan KA, Mednick SC. 2016. Autonomic
39 activity during sleep predicts memory consolidation in humans. *Proc Natl Acad Sci U S A*;
40 **113**:7272–7.
- 41 21. Mednick S, Nakayama K, Stickgold R. 2003. Sleep-dependent learning: A nap is as good as
42 a night. *Nat Neurosci*; **6**:697-8.
- 43 22. McDevitt EA, Duggan KA, Mednick SC. 2015. Rem sleep rescues learning from
44 interference. *Neurobiol Learn Mem*; **122**:51-62.
- 45 23. Grosmark AD, Mizuseki K, Pastalkova E, Diba K, Buzsáki G. 2012. Rem sleep reorganizes
46 hippocampal excitability. *Neuron*; **75**:1001-7.
- 47 24. Feld GB, Born J. 2017. Sculpting memory during sleep: Concurrent consolidation and
48 forgetting. *Curr Opin Neurobiol*; **44**:20-7.
- 49 25. Feld GB, Diekelmann S. 2015. Sleep smart—optimizing sleep for declarative learning and
50 memory. *Front Psychol*; **6**:622.

- 1 26. Lewis PA, Durrant SJ. 2011. Overlapping memory replay during sleep builds cognitive
2 schemata. *Trends in cognitive sciences*; **15**:343-51.
- 3 27. van Dongen EV, Takashima A, Barth M, Zapp J, Schad LR, Paller KA, Fernández G. 2012.
4 Memory stabilization with targeted reactivation during human slow-wave sleep. *Proc Natl Acad Sci*
5 *U S A*; **109**:10575-80.
- 6 28. Rothschild G, Eban E, Frank LM. 2017. A cortical–hippocampal–cortical loop of
7 information processing during memory consolidation. *Nat Neurosci*; **20**:251.
- 8 29. Schreiner T, Rasch B. 2014. Boosting vocabulary learning by verbal cueing during sleep.
9 *Cereb Cortex*:bhu139.
- 10 30. Antony JW, Gobel EW, O'hare JK, Reber PJ, Paller KA. 2012. Cued memory reactivation
11 during sleep influences skill learning. *Nat Neurosci*; **15**:1114-6.
- 12 31. Hu X, Antony JW, Creery JD, Vargas IM, Bodenhausen GV, Paller KA. 2015. Unlearning
13 implicit social biases during sleep. *Science*; **348**:1013-5.
- 14 32. Diekelmann S, Born J. 2015. Cueing fear memory during sleep-to extinguish or to enhance
15 fear? *Sleep*; **38**:337-9.
- 16 33. Diekelmann S, Büchel C, Born J, Rasch B. 2011. Labile or stable: Opposing consequences
17 for memory when reactivated during waking and sleep. *Nat Neurosci*; **14**:381-6.
- 18 34. Diekelmann S, Biggel S, Rasch B, Born J. 2012. Offline consolidation of memory varies
19 with time in slow wave sleep and can be accelerated by cuing memory reactivations. *Neurobiol*
20 *Learn Mem*; **98**:103-11.
- 21 35. Cordi MJ, Diekelmann S, Born J, Rasch B. 2014. No effect of odor-induced memory
22 reactivation during rem sleep on declarative memory stability. *Frontiers in systems neuroscience*; **8**.
- 23 36. Seibold M, Rasch B, Born J, Diekelmann S. 2017. Reactivation of interference during sleep
24 does not impair ongoing memory consolidation. *Memory*:1-8.
- 25 37. Zelano C, Sobel N. 2005. Humans as an animal model for systems-level organization of
26 olfaction. *Neuron*; **48**:431-54.
- 27 38. Rihm JS, Diekelmann S, Born J, Rasch B. 2014. Reactivating memories during sleep by
28 odors: Odor specificity and associated changes in sleep oscillations. *J Cogn Neurosci*; **26**:1806-18.
- 29 39. Klinzing JG, Kugler S, Soekadar SR, Rasch B, Born J, Diekelmann S. 2017. Odor cueing
30 during slow-wave sleep benefits memory independently of low cholinergic tone.
31 *Psychopharmacology (Berl)*:1-9.
- 32 40. Rudoy JD, Voss JL, Westerberg CE, Paller KA. 2009. Strengthening individual memories
33 by reactivating them during sleep. *Science*; **326**:1079-.
- 34 41. Berkers RM, Ekman M, van Dongen EV, Takashima A, Barth M, Paller K, Fernandez G.
35 2017. Cued reactivation during slow-wave sleep induces connectivity changes related to memory
36 stabilization. *bioRxiv*:185611.
- 37 42. Creery JD, Oudiette D, Antony JW, Paller KA. 2015. Targeted memory reactivation during
38 sleep depends on prior learning. *Sleep*; **38**:755-63.
- 39 43. Cairney SA, Lindsay S, Sobczak JM, Paller KA, Gaskell MG. 2016. The benefits of targeted
40 memory reactivation for consolidation in sleep are contingent on memory accuracy and direct cue-
41 memory associations. *Sleep*; **39**:1139-50.
- 42 44. Oudiette D, Antony JW, Creery JD, Paller KA. 2013. The role of memory reactivation
43 during wakefulness and sleep in determining which memories endure. *J Neurosci*; **33**:6672-8.
- 44 45. Fischer S, Diekelmann S, Born J. 2011. Sleep's role in the processing of unwanted
45 memories. *J Sleep Res*; **20**:267-74.
- 46 46. Rauchs G, Feyers D, Landeau B, Bastin C, Luxen A, Maquet P, Collette F. 2011. Sleep
47 contributes to the strengthening of some memories over others, depending on hippocampal activity
48 at learning. *J Neurosci*; **31**:2563-8.
- 49 47. Saletin JM, Goldstein-Piekarski AN, Greer SM, Stark S, Stark CE, Walker MP. 2016.
50 Human hippocampal structure: A novel biomarker predicting mnemonic vulnerability to, and
51 recovery from, sleep deprivation. *J Neurosci*; **36**:2355.

- 1 48. Van Dongen EV, Thielen J-W, Takashima A, Barth M, Fernández G. 2012. Sleep supports
2 selective retention of associative memories based on relevance for future utilization. *PLoS ONE*;
3 7:e43426.
- 4 49. Oyarzún JP, Morís J, Luque D, de Diego-Balaguer R, Fuentemilla L. 2017. Targeted
5 memory reactivation during sleep adaptively promotes the strengthening or weakening of
6 overlapping memories. *J Neurosci*; **37**:7748-58.
- 7 50. Cairney SA, Sobczak JM, Lindsay S, Gaskell MG. 2017. Mechanisms of memory retrieval
8 in slow-wave sleep. *Sleep*; **40**.
- 9 51. Fuentemilla L, Miró J, Ripollés P, Vilà-Balló A, Juncadella M, Castañer S, Salord N,
10 Monasterio C, Falip M, Rodríguez-Fornells A. 2013. Hippocampus-dependent strengthening of
11 targeted memories via reactivation during sleep in humans. *Curr Biol*; **23**:1769-75.
- 12 52. Groch S, Schreiner T, Rasch B, Huber R, Wilhelm I. 2017. Prior knowledge is essential for
13 the beneficial effect of targeted memory reactivation during sleep. *Sci Rep*; **7**:39763.
- 14 53. Schreiner T, Rasch B. 2014. Boosting vocabulary learning by verbal cueing during sleep.
15 *Cereb Cortex*; **25**:4169-79.
- 16 54. Schreiner T, Lehmann M, Rasch B. 2015. Auditory feedback blocks memory benefits of
17 cueing during sleep. *Nat Commun*; **6**:8729.
- 18 55. Schreiner T, Göldi M, Rasch B. 2015. Cueing vocabulary during sleep increases theta
19 activity during later recognition testing. *Psychophysiology*; **52**:1538-43.
- 20 56. Farthouat J, Gilson M, Peigneux P. 2016. New evidence for the necessity of a silent plastic
21 period during sleep for a memory benefit of targeted memory reactivation. *SSCUS*; **1**:14-26.
- 22 57. Batterink LJ, Paller KA. 2015. Sleep-based memory processing facilitates grammatical
23 generalization: Evidence from targeted memory reactivation. *Brain Lang*.
- 24 58. Batterink LJ, Creery JD, Paller KA. 2016. Phase of spontaneous slow oscillations during
25 sleep influences memory-related processing of auditory cues. *J Neurosci*; **36**:1401-9.
- 26 59. Tamminen J, Ralph MAL, Lewis PA. 2017. Targeted memory reactivation of newly learned
27 words during sleep triggers rem-mediated integration of new memories and existing knowledge.
28 *Neurobiol Learn Mem*; **137**:77-82.
- 29 60. Donohue KC, Spencer RM. 2011. Continuous re-exposure to environmental sound cues
30 during sleep does not improve memory for semantically unrelated word pairs. *J Cogn Educ*
31 *Psychol*; **10**:167.
- 32 61. Hennies N, Lambon Ralph MA, Durrant SJ, Cousins JN, Lewis PA. 2017. Cued memory
33 reactivation during sws abolishes the beneficial effect of sleep on abstraction. *Sleep*; **40**:zsx102.
- 34 62. Battaglia FP, Pennartz C. 2011. The construction of semantic memory: Grammar-based
35 representations learned from relational episodic information. *Frontiers in computational*
36 *neuroscience*; **5**:36.
- 37 63. Albouy G, King BR, Maquet P, Doyon J. 2013. Hippocampus and striatum: Dynamics and
38 interaction during acquisition and sleep-related motor sequence memory consolidation.
39 *Hippocampus*; **23**:985-1004.
- 40 64. Debas K, Carrier J, Barakat M, Marrelec G, Bellec P, Tahar AH, Karni A, Ungerleider LG,
41 Benali H, Doyon J. 2014. Off-line consolidation of motor sequence learning results in greater
42 integration within a cortico-striatal functional network. *Neuroimage*; **99**:50-8.
- 43 65. Debas K, Carrier J, Orban P, Barakat M, Lungu O, Vandewalle G, Tahar AH, Bellec P,
44 Karni A, Ungerleider LG. 2010. Brain plasticity related to the consolidation of motor sequence
45 learning and motor adaptation. *Proc Natl Acad Sci U S A*; **107**:17839-44.
- 46 66. Schendan HE, Searl MM, Melrose RJ, Stern CE. 2003. An fmri study of the role of the
47 medial temporal lobe in implicit and explicit sequence learning. *Neuron*; **37**:1013-25.
- 48 67. Laventure S, Fogel S, Lungu O, Albouy G, Sévigny-Dupont P, Vien C, Sayour C, Carrier J,
49 Benali H, Doyon J. 2016. Nrem2 and sleep spindles are instrumental to the consolidation of motor
50 sequence memories. *PLoS Biol*; **14**:e1002429.

- 1 68. Walker MP, Brakefield T, Hobson JA, Stickgold R. 2003. Dissociable stages of human
2 memory consolidation and reconsolidation. *Nature*; **425**:616.
- 3 69. Nishida M, Walker MP. 2007. Daytime naps, motor memory consolidation and regionally
4 specific sleep spindles. *PLoS ONE*; **2**:e341.
- 5 70. Pereira SIR, Bejjamini F, Weber FD, Vincenzi RA, da Silva FAC, Louzada FM. 2017.
6 Tactile stimulation during sleep alters slow oscillation and spindle densities but not motor skill.
7 *Physiol Behav*; **169**:59-68.
- 8 71. Schönauer M, Geisler T, Gais S. 2014. Strengthening procedural memories by reactivation
9 in sleep. *J Cogn Neurosci*; **26**:143-53.
- 10 72. Cousins JN, El-Deredy W, Parkes LM, Hennies N, Lewis PA. 2014. Cued memory
11 reactivation during slow-wave sleep promotes explicit knowledge of a motor sequence. *J Neurosci*;
12 **34**:15870-6.
- 13 73. Cousins JN, El-Deredy W, Parkes LM, Hennies N, Lewis PA. 2016. Cued reactivation of
14 motor learning during sleep leads to overnight changes in functional brain activity and connectivity.
15 *PLoS Biol*; **14**:e1002451.
- 16 74. Diekelmann S, Born J, Rasch B. 2016. Increasing explicit sequence knowledge by odor
17 cueing during sleep in men but not women. *Front Behav Neurosci*; **10**.
- 18 75. Johnsen BH, Thayer JF, Laberg JC, Wormnes B, Raadal M, Skaret E, Kvale G, Berg E.
19 2003. Attentional and physiological characteristics of patients with dental anxiety. *J Anxiety*
20 *Disord*; **17**:75-87.
- 21 76. Kensinger EA, Murray BD. Emotional memory. In: Seel NM, editor. Encyclopedia of the
22 sciences of learning. Boston, MA: Springer US; 2012. p. 1128-31.
- 23 77. Walker MP. 2009. The role of sleep in cognition and emotion. *Ann N Y Acad Sci*; **1156**:168-
24 97.
- 25 78. Genzel L, Spormaker V, Konrad B, Dresler M. 2015. The role of rapid eye movement
26 sleep for amygdala-related memory processing. *Neurobiol Learn Mem*; **122**:110-21.
- 27 79. Cellini N, Torre J, Stegagno L, Sarlo M. 2016. Sleep before and after learning promotes the
28 consolidation of both neutral and emotional information regardless of rem presence. *Neurobiol*
29 *Learn Mem*; **133**:136-44.
- 30 80. Cairney SA, Durrant SJ, Power R, Lewis PA. 2015. Complementary roles of slow-wave
31 sleep and rapid eye movement sleep in emotional memory consolidation. *Cereb Cortex*; **25**:bht349.
- 32 81. Sterpenich V, Schmidt C, Albouy G, Matarazzo L, Vanhaudenhuyse A, Boveroux P,
33 Degueldre C, Leclercq Y, Balteau E, Collette F. 2014. Memory reactivation during rapid eye
34 movement sleep promotes its generalization and integration in cortical stores. *Sleep*; **37**:1061-75.
- 35 82. Lehmann M, Schreiner T, Seifritz E, Rasch B. 2016. Emotional arousal modulates
36 oscillatory correlates of targeted memory reactivation during nrem, but not rem sleep. *Sci Rep*; **6**.
- 37 83. Ashton JE, Cairney SA, Gaskell MG. 2017. No effect of targeted memory reactivation
38 during slow-wave sleep on emotional recognition memory. *J Sleep Res*.
- 39 84. Groch S, McMakin D, Guggenbühl P, Rasch B, Huber R, Wilhelm I. 2016. Memory cueing
40 during sleep modifies the interpretation of ambiguous scenes in adolescents and adults. *Dev Cogn*
41 *Neurosci*; **17**:10-8.
- 42 85. Hauner KK, Howard JD, Zelano C, Gottfried JA. 2013. Stimulus-specific enhancement of
43 fear extinction during slow-wave sleep. *Nat Neurosci*.
- 44 86. He J, Sun H-Q, Li S-X, Zhang W-H, Shi J, Ai S-Z, Li Y, Li X-J, Tang X-D, Lu L. 2015.
45 Effect of conditioned stimulus exposure during slow wave sleep on fear memory extinction in
46 humans. *Sleep*; **38**:423-31.
- 47 87. Rihm JS, Rasch B. 2015. Replay of conditioned stimuli during late rem and stage n2 sleep
48 influences affective tone rather than emotional memory strength. *Neurobiol Learn Mem*; **122**:142-
49 51.

- 1 88. Ai S-Z, Chen J, Liu J-F, He J, Xue Y-X, Bao Y-P, Han F, Tang X-D, Lu L, Shi J. 2015.
2 Exposure to extinction-associated contextual tone during slow-wave sleep and wakefulness
3 differentially modulates fear expression. *Neurobiol Learn Mem*; **123**:159-67.
- 4 89. Cellini N, Parma V. 2015. Commentary: Olfactory aversive conditioning during sleep
5 reduces cigarette-smoking behavior. *Front Psychol*; **6**:586.
- 6 90. Rihm JS, Sollberger SB, Soravia LM, Rasch B. 2016. Re-presentation of olfactory exposure
7 therapy success cues during non-rapid eye movement sleep did not increase therapy outcome but
8 increased sleep spindles. *Front Hum Neurosci*; **10**.
- 9 91. Groch S, Preiss A, McMakin DL, Rasch B, Walitza S, Huber R, Wilhelm I. 2017. Targeted
10 reactivation during sleep differentially affects negative memories in socially anxious and healthy
11 children and adolescents. *J Neurosci*; **37**:2425-34.
- 12 92. Cai DJ, Mednick SA, Harrison EM, Kanady JC, Mednick SC. 2009. Rem, not incubation,
13 improves creativity by priming associative networks. *Proc Natl Acad Sci U S A*; **106**:10130-4.
- 14 93. Ritter SM, Strick M, Bos MW, Van Baaren RB, Dijksterhuis A. 2012. Good morning
15 creativity: Task reactivation during sleep enhances beneficial effect of sleep on creative
16 performance. *J Sleep Res*; **21**:643-7.
- 17 94. Guilford JP. 1967. *The nature of human intelligence*.
- 18 95. Honma M, Plass J, Brang D, Florczak SM, Grabowecky M, Paller KA. 2016. Sleeping on
19 the rubber-hand illusion: Memory reactivation during sleep facilitates multisensory recalibration.
20 *Neuroscience of consciousness*; **2016**.
- 21 96. Sereno MI, Huang R-S. 2014. Multisensory maps in parietal cortex. *Curr Opin Neurobiol*;
22 **24**:39-46.
- 23 97. Tonetti L, Cellini N, de Zambotti M, Fabbri M, Martoni M, Fábregas SE, Stegagno L,
24 Natale V. 2013. Polysomnographic validation of a wireless dry headband technology for sleep
25 monitoring in healthy young adults. *Physiol Behav*; **118**:185-8.
- 26 98. Cellini N, McDevitt EA, Ricker AA, Rowe KM, Mednick SC. 2015. Validation of an
27 automated wireless system for sleep monitoring during daytime naps. *Behav Sleep Med*; **13**:157-68.
- 28 99. Schouten DI, Pereira SI, Tops M, Louzada FM. 2017. State of the art on targeted memory
29 reactivation: Sleep your way to enhanced cognition. *Sleep Med, Rev*; **32**:123-31.
- 30 100. Bellesi M, Riedner BA, Garcia-Molina GN, Cirelli C, Tononi G. 2014. Enhancement of
31 sleep slow waves: Underlying mechanisms and practical consequences. *Frontiers in systems
32 neuroscience*; **8**.
- 33 101. Schreiner T, Rasch B. 2017. The beneficial role of memory reactivation for language
34 learning during sleep: A review. *Brain Lang*; **167**:94-105.
- 35 102. Ngo H-VV, Martinetz T, Born J, Mölle M. 2013. Auditory closed-loop stimulation of the
36 sleep slow oscillation enhances memory. *Neuron*; **78**:545-53.
- 37 103. Ngo H-VV, Miedema A, Faude I, Martinetz T, Mölle M, Born J. 2015. Driving sleep slow
38 oscillations by auditory closed-loop stimulation—a self-limiting process. *J Neurosci*; **35**:6630-8.
- 39 104. Santostasi G, Malkani R, Zee P, Paller K. 2015. A phase-locked loop for acoustic
40 stimulation during slow-wave sleep *Sleep*; **38**:A98.
- 41 105. Ong JL, Lo JC, Chee NI, Santostasi G, Paller KA, Zee PC, Chee MW. 2016. Effects of
42 phase-locked acoustic stimulation during a nap on eeg spectra and declarative memory
43 consolidation. *Sleep Med*; **20**:88-97.
- 44 106. Leminen MM, Virkkala J, Saure E, Paajanen T, Zee PC, Santostasi G, Hublin C, Müller K,
45 Porkka-Heiskanen T, Huutilainen M. 2017. Enhanced memory consolidation via automatic sound
46 stimulation during non-rem sleep. *Sleep*; **40**.
- 47 107. Shimizu R, Connolly P, Cellini N, Armstrong D, Hernandez L, Estrada R, Aguilar M,
48 Weisend M, Mednick SC, Simons S. *Under Review*. Closed-loop targeted memory reactivation
49 during sleep improves spatial navigation.
- 50 108. Antony J, Piloto LR, Wang M, Pacheco P, Norman KA, Paller KA. 2017. Sleep spindle
51 refractoriness segregates periods of memory reactivation. *bioRxiv*:235606.

- 1 109. Lustenberger C, Patel Y, Alagapan S, Page J, Price B, Boyle M, Frohlich F. 2017. High-
2 density eeg characterization of brain responses to auditory rhythmic stimuli during wakefulness and
3 nrem sleep. *Neuroimage*.
- 4 110. Cellini N. 2017. Memory consolidation in sleep disorders. *Sleep Med, Rev*; **35**:101-12.
- 5 111. Mander BA, Santhanam S, Saletin JM, Walker MP. 2011. Wake deterioration and sleep
6 restoration of human learning. *Curr Biol*; **21**:R183-R4.
- 7 112. Paller KA. 2017. Sleeping in a brave new world: Opportunities for improving learning and
8 clinical outcomes through targeted memory reactivation. *Current Directions in Psychological*
9 *Science*:0963721417716928.

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