Review

Upgrading the sleeping brain with targeted memory reactivation

Delphine Oudiette and Ken A. Paller

Department of Psychology and Cognitive Neuroscience Program, Northwestern University, Evanston, IL, USA

A fundamental feature of human memory is the propensity for beneficial changes in information storage after initial encoding. Recent research findings favor the possibility that memory consolidation during sleep is instrumental for actively maintaining the storehouse of memories that individuals carry through their lives. The information that ultimately remains available for retrieval may tend to be that which is reactivated during sleep. A novel source of support for this idea comes from demonstrations that neurocognitive processing during sleep can benefit memory storage when memories are covertly cued via auditory or olfactory stimulation. Investigations of these subtle manipulations of memory processing during sleep can help elucidate the mechanisms of memory preservation in the human brain.

> 'When from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, still, alone, more fragile, but with more vitality, more unsubstantial, more persistent, more faithful, the smell and taste of things remain poised a long time, like souls, ready to remind us, waiting and hoping for their moment, amid the ruins of all the rest; and bear unfaltering, in the tiny and almost impalpable drop of their essence, the vast structure of recollection.' [Translated from French].
>
> Marcel Proust, *In Search of Lost Time*, 1913

Memory consolidation during sleep

The ability to store and recall information undergirds all human knowledge. The essential transactions in the brain occur not only at acquisition and retrieval, but also during the intervening time – including sleep.

During this intervening time period, changes in how information is stored in the brain contribute to memory consolidation (see Glossary) [1,2]. With respect to memory for facts and events, for example, consolidation may entail rehearsal of newly acquired information and associations with other stored information – and as the cortical networks of memory storage change, the new information can potentially become more stable and enduring.

During sleep, stored information does not remain sedentary, but rather may receive regular exercise, which changes it and potentially preserves it [3–5]. Consolidation may thus progress overnight, perhaps as a function of the extent to which specific memories are reactivated during sleep. In this review, we describe how the method of targeted memory reactivation (TMR) provides novel perspectives on how the sleeping brain contributes to memory.

Spontaneous reactivation during sleep

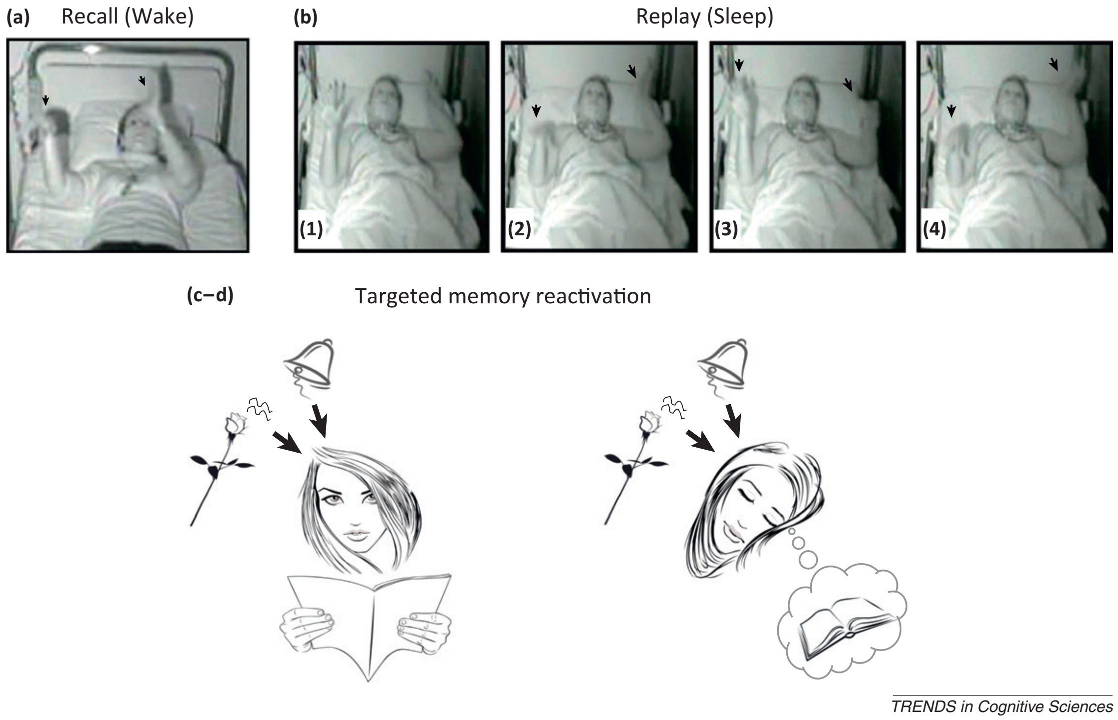
Some of the most convincing evidence linking sleep and memory comes from observations of hippocampal place-cell activity in rodents during sleep [6,7]. During this presumptive 'memory replay', the temporal sequence of place-cell activity recapitulates activity during exploration [8,9]. Place-cell reactivation occurs preferentially in slow-wave sleep (SWS) [7,10], sometimes in a temporally compressed manner [11], and often in conjunction with hippocampal field-potential oscillations known as sharp-wave ripples [12]. Comparable sleep reactivation has also been observed in other brain areas [13–15] and likely occurs in many other species [16,17]. Hippocampal reactivations are thought to be orchestrated at a neocortical level by slow neural oscillations during SWS. According to this idea, the depolarizing up-phases of the slow oscillations drive the formation of spindle-ripple events (sharp-wave ripples

Glossary

Declarative memory: recall and recognition of facts and episodes.
Memory consolidation: a gradual process of change in memory storage, sometimes including distortion, loss of details, and/or integration with other information, that is essential for newly acquired information to ultimately become enduring.
Non-rapid eye movement (NREM) sleep: accounts for 75% of the total sleep time and comprises sleep stage 1 (sleep onset), sleep stage 2, and SWS.
Rapid eye movement (REM) sleep: predominant in the late period of nocturnal sleep, characterized by fast and low-voltage EEG, rapid (saccadic) eye movements, and muscle paralysis (atonia).
Ripples: fast oscillations of hippocampal field potentials (150-200 Hz), often associated with hippocampal sharp-waves and occurring during SWS and quiet wake states.
Sleep stage 2 (or NREM2): light sleep; predominant sleep stage during a normal night of sleep, containing characteristic EEG features such as spindles, K complexes, and occasional slow waves.
Sleep learning: the acquisition of new information through sensory stimulation during sleep.
Slow wave sleep (SWS or NREM3): deep sleep, predominant in the early period of nocturnal sleep, characterized by ample slow waves in the delta frequency band (<4 Hz).
Slow oscillations: cortical oscillations at 1 Hz or less, comprising a hyperpolarization phase (down) and a depolarization phase (up); the up phase is conducive to neuronal activity and presumed to facilitate hippocampal-neocortical interaction and consolidation.
Spindles: brief bursts of EEG oscillations in the sigma band (12-15 Hz), lasting approximately 0.5-2 s and thought to correspond to some sort of memory processing.
Targeted memory reactivation (TMR): a method whereby cues associated with previous learning are used to externally reactivate aspects of this learning.

Corresponding author: Paller, K.A. (kap@northwestern.edu).

1364-6613/$ – see front matter
http://dx.doi.org/10.1016/j.tics.2013.01.006



TRENDS in Cognitive Sciences

Figure 1. A demonstration of spontaneous memory reactivation and a schematic illustration of targeted memory reactivation. Photographs were extracted from video recordings during the execution of a learned sequence of arm movements and during subsequent sleep (adapted from [27]; see supplementary video 2). **(a)** A control subject acted out the sequence while awake. **(b)** A sleepwalker exhibited replay of the structured sequence during SWS, thus providing the first direct documentation of memory reactivation during sleep in humans (the fourth panel maps on to the position shown during learning). In a typical protocol for targeted memory reactivation during sleep, the same stimuli are presented **(c)** in association with learning and **(d)** during sleep. Elements of panels (**c**) and (**d**) were taken from iStockphoto.

temporally nested into troughs of spindles). The depolarizing down-phases of the slow oscillations, by contrast, are moments of relative neuronal quiescence. Spindle-ripple events grouped during slow oscillations may play a key role in hippocampal-neocortical dialogue during sleep [18–21]. As a result, consolidation may proceed, as memories initially dependent on both the hippocampus and the neocortex may come to be preferentially dependent on neocortical storage [2].

Although direct evidence showing that hippocampal reactivation of place cells patterns plays a causal role in memory consolidation is lacking, this hypothesis has some indirect support. For example, hippocampal ripples increase after learning, with a concomitant improvement in performance [22], and selective suppression of ripples impairs memory performance [23].

In human neuroimaging studies, brain activations linked to motor skill learning and spatial navigation are recapitulated during post-training sleep, with correlations between level of activation and memory improvement [24,25]. Hippocampal ripples were detected via intracranial recordings in epileptic patients during a nap and during quiet wakefulness, and ripple activity in adjacent cortex correlated with subsequent recall, suggesting a relationship to consolidation [26]. This ripple activity may be a sign of memory reactivation corresponding to previous learning, even though it lacks the specific link with stored information evident in place-cell memory replay. Still, a specific demonstration of spontaneous memory replay was captured on video (Figure 1a,b) when a sleepwalker acted out a recently trained motor sequence [27].

The purpose of spontaneous reactivation

Which memories, among a vast set of stored memories, are reactivated during sleep and thereby less likely forgotten? Animal studies indicate that sleep may accentuate consolidation preferentially for useful memories. First, reward-related information was more likely to be replayed than non-rewarded information [28]. Second, rats tended to reactivate more newly learned locations during sleep than old locations, and the amount of goal-related reactivation correlated with memory performance [29]. Third, after a rat acquired new rules, prefrontal activity that occurred conjointly with hippocampal ripples during sleep reflected the neural patterns during the training, particularly those displayed at the decision point [15]. Thus, spontaneous reactivation during sleep tended to concern episodes relevant for the future.

Spontaneous reactivation may also play a role in cognitive development. This question has been explored extensively in juvenile songbirds learning to sing [30]. After exposure to an adult tutor song, bursting activity is apparent during subsequent sleep in forebrain premotor neurons; apparently sleeping birds spontaneously recapitulate the song template. This spontaneous reactivation was contingent on prior singing practice, during which the birds heard their own auditory feedback. This requirement suggests that spontaneous reactivation during sleep was a part of the normal learning process.

In humans, there is no direct demonstration showing whether or not sleep replay preferentially targets particular types of memories. However, evidence that encoding factors can reinforce sleep-dependent consolidation indirectly supports the selective replay hypothesis. Emotionally salient stimuli [31,32], intention to remember [33], and anticipation of a future reward if material is correctly remembered [34] all reinforced the beneficial effect of sleep on memory consolidation. Furthermore, after the explicit instruction to encode some items and to forget others, sleep consolidation was biased toward to-be-remembered items [35,36]. These studies suggest that sleep-dependent memory consolidation involves a discriminatory mechanism, but it remains to be demonstrated that sleep reactivation is responsible for the selectivity.

Does spontaneous reactivation preserve memory storage in strict accordance with an individual's future needs? Perhaps reactivation is suboptimal and subject to some neural randomness, as might be deduced from dream content. Indeed, memory consolidation need not be solely a function of intrinsic reactivation – it can be systematically guided during sleep.

Controlling reactivation: early efforts

To what extent can one select the specific memories reactivated during sleep? Well before the discovery of memory replay, several studies foresaw that consolidation could be altered during sleep by presenting the sleeper with cues to recent learning [37].

In a classical-conditioning paradigm in rats, a subtle ear-shock repeatedly preceded an unpleasant foot-shock, such that ear-shock alone came to elicit fear responses [38]. If rats then received ear-shock during rapid eye movement (REM) sleep, conditioned fear responses were augmented. When ear-shocks were presented during SWS instead, conditioning was lessened [39].

In humans, a complex logic task was learned in the context of a ticking clock, and the sound was presented again during REM sleep (concurrently with eye movements) to produce a 23% performance improvement one week later [40]. Similarly, auditory stimulation applied during eye movements in REM sleep improved performance in a Morse code task that was presented with an auditory sequence during wake in five subjects [41]. In another study, participants viewed 20 objects and then, during sleep, spoken names of half of the objects were presented [42]. When these sound cues were applied during REM sleep, the expected memory benefits were not observed. However, when applied during stage 2 sleep, both recall and recognition improved for cued objects compared to uncued objects.

Despite these promising early results and other findings on sleep stimulation (Box 1), the possibilities for memory manipulation during sleep were largely neglected until recently. In part, this research was tinged by associations with 'sleep learning', which was soundly criticized as an artifact of stimulation during brief periods of waking, because studies often lacked electrophysiological verification of sleep [37,43]. Building a persuasive literature on TMR requires adequate measures of both electrophysiology and behavior, along with a solid theoretical foundation.

Context-cued and item-cued reactivation during SWS

Nourished by prior evidence implicating SWS in declarative memory, the idea of influencing memory consolidation during sleep blossomed in 2007 due to the landmark study by Rasch and colleagues [44]. Participants learned paired object-location associations while smelling a rose odor. They then slept, and when they exhibited SWS the researchers administered puffs of rose-scented air (with no signs of sleep disruption in EEG recordings). Recall was improved compared to that in participants who did not receive odors during SWS (or who received odors during SWS, but not during learning). Neuroimaging in other participants showed odor-cued hippocampal activation during sleep after learning. Odors likely triggered reactivation of the training context, which then benefitted corresponding spatial memories. However, this study did not address the specificity with which some memories might be selectively reactivated and strengthened.

Rudoy and colleagues used auditory cues to demonstrate that memory processing during sleep could be highly specific [45]. Participants first learned object–location associations. Each object was shown together with its characteristic sound (e.g., door – creak, dog – bark). After

Box 1. Sensory processing during sleep

Individuals are seemingly dead to the world during sleep, with their senses effectively shut down so that only the strongest stimuli influence them – TMR compellingly belies this common belief. That meaningful stimuli delivered during sleep can occasionally be incorporated into dreams has been known at least as far back as Aristotle. Yet, the scope and potential effects of sensory processing independent of the sleeper's awareness of this processing have only begun to be revealed.

Odors rarely awaken sleepers [57]; noxious odors or those of a predator do not modify autonomic responses [57,58]; and do not trigger EEG activation even when applied in high concentration [57,59]. Nevertheless, arousal can be triggered by strong odors that simultaneously activate olfactory and trigeminal pathways [60].

Odors that do not trigger arousal can still have an impact. Lavender odors mildly improve sleep quality in women [61]. Odors elicit brain potentials during sleep with longer latencies and larger amplitudes than during wakefulness [62]. Odors during sleep transiently modify breathing patterns in humans [59] and induce sniffing responses in infant rats [63].

Sounds during sleep are generally more arousing than odors. Arousal thresholds are higher during SWS than stage 2 or REM sleep [64], decrease as the night unfolds [65], and are lower for meaningful stimuli, such as one's own name [66]. The auditory brainstem response is not altered during sleep [67], although subsequent brain potentials are [68,69]. Robust cognitive event-related potentials (ERPs) are especially evident during REM sleep, which suggests deep processing of conspicuous stimuli, but whether such effects occur in other stages is controversial [68,69]. Neuronal firing rates in primary and secondary auditory cortex in monkeys either increase or decrease during sleep, whereas overall neuronal activity is fairly similar to that in wakefulness [70]. Yet, sensitivity is reduced in primary auditory cortex, as responses to quiet sounds are weaker during SWS compared to waking [71].

A neuroimaging study showed comparable activation during NREM sleep and waking; beeps activated auditory cortex, caudate, and thalamus, whereas the participant's own name additionally activated language regions [72]. However, auditory cortex responses to a story or music in another study were reduced during sleep compared with wakefulness [73]. Given that sounds during sleep elicited responses in the thalamus and auditory cortex only when spindles were absent [74,75] and that cortical responses depended on phase of slow oscillations [75], it may be important to take such fluctuations in sleep physiology into account in order to appreciate fully potential sensory processing during sleep.

learning, participants took a nap. While asleep, they were exposed to half of the sounds from the learning phase at a low intensity, with no sleep disruption or knowledge of the stimulation *per se* evident later. Upon waking, participants recalled locations more accurately for objects cued during sleep than for objects not cued during sleep. This TMR demonstration shows that reminders during sleep can be used to target the reactivation and strengthening of individual memories.

Scope of TMR

Many questions remain about the boundary conditions for applying TMR to yield convincing results. First, creating an association between learning and cues to be used as offline reminders is a requirement for effective TMR (Figure 1c,d); applying the cues alone, without a previous association with learning, does not have any beneficial effect on memory [44].

In the case of auditory stimuli, it is unknown whether sounds must be congruent with learning [45] or whether arbitrary sounds are effective. Wide-ranging applications of TMR would be possible if any sound can be linked with any learning. A study using contextual sounds during learning and sleep illustrates several potential pitfalls for such investigations [46]. First, sounds may be ineffective if they are too commonplace, such that they are prone to many conceptual associations in addition to a new link to recent learning. Second, learning measures must be sufficiently sensitive to potential benefits. Also, sensory habituation with continuous exposure may limit the extent to which reactivation is promoted. Studies taking these considerations into account are needed to characterize the potential effectiveness of TMR.

Whereas TMR has produced boosts for visuospatial learning (a common example of declarative memory), Antony and colleagues found that TMR can also strengthen skill learning [47]. Volunteers learned to play two short melodies by pressing four keys in time with repeating 12-item sequences of moving circles (resembling the game *Guitar Hero*; see supplementary video 1). After learning, one melody was softly presented during SWS. After sleep, participants were reliably more accurate when performing the melody cued during sleep than when performing the one not cued.

Some cues and some tasks may be more suitable for TMR than others. Indeed, a standard type of procedural learning was not changed by re-exposing participants to odor cues during sleep [44]. Sounds tightly associated with learned action patterns may be particularly beneficial for evoking sensorimotor integration during sleep [47].

Most recent TMR studies have focused on SWS, so it is difficult to make generalizations about other sleep stages. In the study by Rasch and colleagues [44], the application of rose odor during REM sleep failed to produce performance gains for recall of object locations or for procedural learning. Nevertheless, these results do not exclude the possibility of other benefits from cuing during REM sleep, perhaps for emotional memory or integrative learning. Additional studies of TMR during stage 2 sleep are also needed, despite early indications of beneficial outcomes [42].

TMR during sleep versus during wakefulness

Even though rehearsal is undoubtedly helpful for improving memory during waking, TMR during waking does not always benefit memory [44,45,47]. Diekelmann and colleagues specifically contrasted TMR during SWS versus wakefulness [48]. They found that an interference task performed just after odor-triggered reactivation weakened spatial memories during wakefulness, but not during SWS. They concluded that wake TMR returned memories to a labile state of increased susceptibility to interference, whereas sleep TMR stabilized memories, making them resistant to interference. Alternatively, it is plausible that wake TMR exacerbated interference by shortening the effective distance between the two learning periods (merging memories for odor-cued associations and interference associations), whereas the wake protocol for initial learning and interference without odors helped participants to mentally segregate the associations, due to the long, uninterrupted interval prior to the interference task. In a recent study, Oudiette and colleagues targeted the reactivation of low-value associations during wakefulness and observed a subsequent improvement for these memories compared to other low-value associations, arguing against the destabilization hypothesis of wake reactivation of spatial memories [49].

Neural mechanisms of TMR

We explain TMR effects by supposing that external cues cause covert memory reactivation; this hypothesis now has empirical confirmation [50]. In this study, rats were trained to run either left or right in response to rising or falling tones, respectively. Afterwards, when sounds were played during SWS, hippocampal place cells associated with either side were preferentially reactivated by the corresponding tone. Interestingly, the overall number of reactivation events was not increased, indicating that there may be a limited capacity for memory reactivation; hippocampal replay was thus biased in accordance with learned associations. Similarly, the application of a bird's own song during sleep triggered a firing pattern in premotor neurons identical to that exhibited during song production [16].

How does TMR facilitate memory? One possibility is that memory reactivation *per se* is sufficient to improve subsequent retrieval, because reactivation necessarily entails strengthening of previous storage (to the extent that the reactivation is veridical [51]). In this case, the longer one sleeps, the more memory reactivation takes place, and so memory benefits are greater. This idea is consistent with results showing equivalent memory benefits of a 40-minute sleep period with odor TMR and a 90-minute sleep period without TMR, because only in the second condition was the memory benefit correlated with time spent in SWS [52]. This study suggests that SWS duration and amount of memory reactivation are critical factors for memory consolidation.

Alternatively, reactivation may be only the beginning of a chain of events that improves memory storage. In one recent study, correct memory judgments about emotionally negative pictures were made faster if the associated sounds had been presented during SWS, but only if SWS duration

Box 2. Externally manipulating sleep patterns

Through several innovative approaches, researchers have attempted to reinforce sleep features, such as slow-waves and spindles, so as to indirectly boost memory reactivation. The methods used include transcranial application of oscillating potentials, transcranial magnetic stimulation (TMS), and acoustic stimulation. Advancing this agenda further, it may one day be possible to rely on computerized control of sleep physiology to optimally drive the brain through stages, adding new meaning to the 'power nap' and allowing humans to reliable get more out of their time asleep.

In one study, TMS pulses at a slow oscillation frequency ($<$1 Hz) were administered to sleeping participants, which resulted in a boost in slow-wave activity both locally and globally over the scalp [76]. Theoretically, an artificial increase of slow oscillations would reinforce sleep-dependent memory consolidation if it engaged appropriate physiological mechanisms.

This prediction was confirmed in another study, in which oscillating electrical currents at 0.75 Hz were applied over lateral frontal regions during NREM sleep [77]. This stimulation protocol increased both slow oscillation power and spindle power compared to sham stimulation. A significant improvement was found in two different declarative memory tasks in conjunction with the EEG effects.

Acoustic stimulation administered at 0.8 Hz constituted a less-invasive way to entrain slow-wave activity [78]. Furthermore, acoustic stimulation can be controlled on the basis of concurrent detection of slow waves, such that automatic enhancement of slow waves can be produced via a closed-loop system (Ngo *et al.*, unpublished). Other studies used acoustic stimuli to suppress slow-wave activity, thereby preventing sleep-dependent gains in texture-discrimination learning [79] or in a visuo-motor task [80]. Boosting or suppressing slow waves during post-training sleep can thus have profound ramifications for subsequent memory. If such methods can be combined with TMR techniques in the future, they may yield even more pronounced memory effects.

Interestingly, various pre-sleep manipulations [81–83] can also cause local slow-wave changes during subsequent sleep. One explanation, based on the synaptic-homeostasis hypothesis, is that the net increase of synaptic strength induced by wake activities is compensated by local synaptic downscaling in the same areas during sleep [84]. An alternative, but not necessarily contradictory, explanation is that local slow-wave modulations due to pre-sleep manipulations could orchestrate spindle-ripple events [18] and, thus, produce a higher level of sleep reactivation. If so, this mechanism may tend to make sleep-dependent memory reinforcement congruent with previous experience, and perhaps also with future needs.

Box 3. Can dream content be manipulated?

A central premise of the movie *Inception* is that espionage in the future will involve infiltrating the dreams of important people. How far is this fictional situation from reality?

Pre-sleep manipulations:

Steps taken during waking could determine the course of a subsequent dream, but the extant results are mixed. Early studies found no notable effect on dreams after erotic deprivation [85] or thirst induction [86]. Whereas a dream comprising a full replay of the day's events is extremely rare, incorporation of some information from the prior day is frequent [87]. After wearing goggles that filter out wavelengths other than red every waking moment for a week, subjects reported that their dreams were tinted in the same reddish hue, the goggle color permeating more and more REM periods as the week went by [88]. Intensively playing a videogame before sleep leads to incorporation of game images in subsequent dreams, even in amnestic patients, who did not remember playing [89]. Task-related images become more abstract in replay episodes across the night [90]. Suppressing thoughts about a person before sleep prompts people to report increased dreaming about this person, a variation of the white-bear effect [91].

Within-sleep manipulations:

Some investigators have attempted to directly manipulate dreams while the subject was asleep. Although never spectacular, effects were still evident. In an early study [86], a water spray during sleep was incorporated in 42% of subsequent dreams (e.g., showers), a flashing light in 23% (e.g., falling stars), and tones in 9% (e.g., a plane crash). Dream context could also be influenced by rocking the bed [92], mild pain [93], electrical stimuli [94], and olfactory stimuli [95]. A conditioning manipulation during sleep provided an elegant demonstration that one could externally modify dream content; the application of a fear-conditioned cue during NREM sleep significantly affected the valence of dreamed emotion [96]. After being trained to navigate in a virtual maze, a few participants dreamt of some task elements; and dreaming of the task was associated with subsequent performance improvements [97]. Similarly, Antony and colleagues observed anecdotal evidence of task-associated dreaming that correlated with a large gain in performance accuracy for a melody that was presented during sleep [47].

was included as a covariate in the analysis (Cairney *et al.*, unpublished). Perhaps memory reactivation starts a process that comes to fruition during subsequent SWS, but these unpublished results must be substantiated and other experimental manipulations applied to directly test this idea.

Finally, TMR success for spatial associations may rely on modulating the activity and connectivity of parahippocampal cortex [53]. When presented during SWS, sounds linked to specific object locations elicited increased right parahippocampal activity compared to control sounds. Although sound cues during SWS did not produce a reliable behavioral benefit in this study (perhaps because subjects were actively inhibiting auditory input due to the loud scanner noise), cue-related activity in bilateral thalamus, cerebellum, and medial temporal lobe, as well as connectivity between cuneus and parahippocampal cortex, predicted degree of memory preservation for cued associations.

Modifying the course of memory consolidation

It is now clear that memory reactivation during sleep can strengthen particular memories. However, it is unclear why particular memories are selected for reactivation. To study reactivation bias, Oudiette and colleagues adopted a directed-remembering procedure during spatial learning, simulating the fact that the things individuals learn each day vary in their future value. Across a retention interval that included a 90-minute nap, recall accuracy declined to a greater extent for low-value than for high-value items. However, low-value memories were rescued by externally triggering their reactivation during the nap [49]. This outcome suggests that reactivation governs the destiny of individual memories, in that memories reactivated during sleep have an increased chance to survive.

If TMR can be used to add new information to existing memories, possibilities for sleep learning might be resuscitated. For example, Arzi and colleagues [54] paired different tones with either a pleasant or an unpleasant odor during sleep and tested whether participants learned this association by measuring sniff responses during subsequent wakefulness. Sniff responses to tones alone were modulated by conditioned valence (more sniffing for pleasant-odor-associated tones). However, nearly all participants showed some arousal surrounding tone

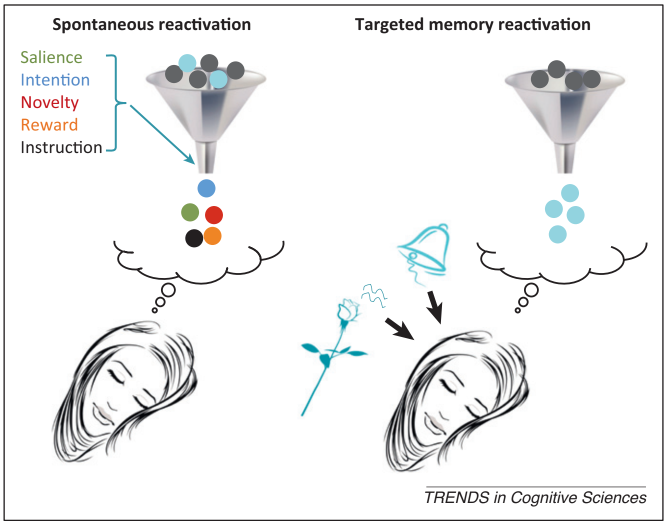


Figure 2. Schematic representation of how selective filtering via sleep reactivation could determine the ultimate status of memory storage. **(a)** Important memories – as determined by emotional salience, intention to remember, novelty, reward, explicit instruction, and other factors – are preferentially replayed and reinforced during sleep, perhaps through spread of activation from higher-order goals and concerns. Memories not sufficiently benefiting from this sleep reactivation tend to be forgotten (memories depicted in grey and light blue color). Accordingly, we propose that memory reactivation during sleep could have a strong influence on which memories remain available in the long run. **(b)** TMR enables another level of control of selective filtering, whereby particular memories will be reactivated and corresponding memory storage strengthened. For example, if the odor or sound corresponding to the light blue memories was applied during sleep, this action would trigger their replay and secure their preservation. Elements of this figure were taken from iStockphoto.

presentations, raising the possibility that awakenings had some influence on the learning effect. Still, novel variants on TMR are worthy of exploration, building on the early TMR studies of conditioning cited above. Furthermore, technical advances may facilitate the future use of TMR in conjunction with other ways to modulate the sleeping brain (Box 2).

Beyond the scope of this review stands the fascinating question of whether one's dream experiences play a role in sleep-dependent memory consolidation. Given that dreams can be composed of pieces of previous waking events, or of conceptually related ideas, discrete connections made between recent and remote memories during dreams might be central for both consolidation and problem solving [55,56], but this hypothesis requires further empirical verification. Whether TMR could influence dream content is addressed in Box 3.

Concluding remarks

In sum, covert memory reactivation during sleep can promote consolidation and thus shape the memory storehouse that each individual possesses. Of the large amount of information people are confronted with each day, what determines which information will be kept and which will be lost? Our proposal is that spontaneous sleep reactivation, based in part on the future relevance of the information, has a powerful impact on memory stability over the long term. TMR can potentially optimize this natural process and thereby help individuals to guide the fate of their stored memories in accordance with their future goals (Figure 2). Moreover, experimental manipulations that promote memory reactivation provide a promising way to probe these neurocognitive mechanisms (see also Box 4).

Box 4. Questions for future research

Mechanisms:

- What neural mechanisms support TMR and how much do they overlap with neural mechanisms of memory consolidation generally?
- What factors govern the selection of specific information for sleep reactivation? Can intentions activated just prior to sleep perpetuate specific types of sleep reactivation?
- Does reactivation come into play for remote memories? How does reactivation differ for recent versus remote memories and how are recent and remote memories integrated during sleep?
- Does reactivation entail an exact replay from learning or does it include distorted recall that could be perpetuated to produce subsequent mis-remembering [51]? Does reactivation exactly reflect what has been learned (see [16], which showed that sleep replay slightly varied from the original tutor song in young birds)?

Methodological considerations:

- Can neurophysiological signatures of reactivation be observed and validated in humans?
- What moments are most conducive for TMR (which sleep stages, what phase of slow waves, and what temporal relationship to spindle activity)?
- Can repeated TMR produce benefits that are large, cumulative, and enduring?
- Is TMR effective with a wide variety of cues? Are verbal cues better or worse than nonverbal cues? Does presenting the spoken name of the participant enhance TMR [37]?
- Why do some sounds wake the sleeper, some provoke a K-complex, and some leave no trace on the EEG?
- To what extent is the response to TMR a function of critical individual differences (W.H. Johnson, PhD thesis, Northwestern University, 1972)?
- Does TMR have any negative side effects (e.g., decreasing the restorative effects of sleep or weakening other, potentially important memories)?
- How might TMR modify sleep cognition as sampled after awakenings from various sleep stages?

Potential clinical or practical benefits:

- Can novel combinations of memory fragments activated during sleep lead to creative insights and can creativity be triggered in this way via TMR [98]?
- Using TMR, can moods and emotions be manipulated, therapies for pathological conditions supplemented, or bad habits (e.g., drug cravings or maladaptive fears) transformed?
- Can TMR erase painful features of a bad memory (Hauner *et al.*, unpublished; Rolls *et al.*, unpublished) or otherwise distort a memory?
- Could old, largely forgotten memories be resuscitated? Can TMR improve memory in people with memory lapses due to aging or disease [99]?

Acknowledgements

We thank Jay Gottfried and two anonymous reviewers for helpful comments, and the National Science Foundation (grant BCS1025697), the AXA Research Fund, and the Bettencourt Schueller Foundation for financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tics.2013.01.006.

References

1 McGaugh, J.L. (2000) Memory – a century of consolidation. *Science* 287, 248–251
2 Paller, K.A. (2009) Memory consolidation: systems. In *Encyclopedia of Neuroscience* (Squire, L.R., ed.), pp. 741–749, Academic Press

3 Diekelmann, S. and Born, J. (2010) The memory function of sleep. *Nat. Rev. Neurosci.* 11, 114–126

4 Saletin, J.M. and Walker, M.P. (2012) Nocturnal mnemonics: sleep and hippocampal memory processing. *Front. Neurol.* 3, 59

5 Stickgold, R. (2005) Sleep-dependent memory consolidation. *Nature* 437, 1272–1278

6 Pavlides, C. and Winson, J. (1989) Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *J. Neurosci.* 9, 2907–2918

7 Wilson, M.A. and McNaughton, B.L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* 265, 676–679

8 Skaggs, W.E. and McNaughton, B.L. (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science* 271, 1870–1873

9 Lee, A.K. and Wilson, M.A. (2002) Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36, 1183–1194

10 Sutherland, G.R. and McNaughton, B. (2000) Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Curr. Opin. Neurobiol.* 10, 180–186

11 Nadasdy, Z. *et al.* (1999) Replay and time compression of recurring spike sequences in the hippocampus. *J. Neurosci.* 19, 9497–9507

12 Buzsaki, G. *et al.* (1992) High-frequency network oscillation in the hippocampus. *Science* 256, 1025–1027

13 Ji, D. and Wilson, M.A. (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. *Nat. Neurosci.* 10, 100–107

14 Pennartz, C.M. *et al.* (2004) The ventral striatum in off-line processing: ensemble reactivation during sleep and modulation by hippocampal ripples. *J. Neurosci.* 24, 6446–6456

15 Peyrache, A. *et al.* (2009) Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. *Nat. Neurosci.* 12, 919–926

16 Dave, A.S. and Margoliash, D. (2000) Song replay during sleep and computational rules for sensorimotor vocal learning. *Science* 290, 812–816

17 Amzica, F. *et al.* (1997) Instrumental conditioning of fast (20- to 50-Hz) oscillations in corticothalamic networks. *Proc. Natl. Acad. Sci. U.S.A.* 94, 1985–1989

18 Molle, M. and Born, J. (2011) Slow oscillations orchestrating fast oscillations and memory consolidation. *Prog. Brain Res.* 193, 93–110

19 Siapas, A.G. and Wilson, M.A. (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21, 1123–1128

20 Sirota, A. *et al.* (2003) Communication between neocortex and hippocampus during sleep in rodents. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2065–2069

21 Steriade, M. (2006) Grouping of brain rhythms in corticothalamic systems. *Neuroscience* 137, 1087–1106

22 Ramadan, W. *et al.* (2009) Hippocampal sharp wave/ripples during sleep for consolidation of associative memory. *PLoS ONE* 4, e6697

23 Girardeau, G. *et al.* (2009) Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.* 12, 1222–1223

24 Maquet, P. *et al.* (2000) Experience-dependent changes in cerebral activation during human REM sleep. *Nat. Neurosci.* 3, 831–836

25 Peigneux, P. *et al.* (2004) Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron* 44, 535–545

26 Axmacher, N. *et al.* (2008) Ripples in the medial temporal lobe are relevant for human memory consolidation. *Brain* 131, 1806–1817

27 Oudiette, D. *et al.* (2011) Evidence for the re-enactment of a recently learned behavior during sleepwalking. *PLoS ONE* 6, e18056

28 Lansink, C.S. *et al.* (2009) Hippocampus leads ventral striatum in replay of place-reward information. *PLoS Biol.* 7, e1000173

29 Dupret, D. *et al.* (2010) The reorganization and reactivation of hippocampal maps predict spatial memory performance. *Nat. Neurosci.* 13, 995–1002

30 Shank, S.S. and Margoliash, D. (2009) Sleep and sensorimotor integration during early vocal learning in a songbird. *Nature* 458, 73–77

31 Hu, P. *et al.* (2006) Sleep facilitates consolidation of emotional declarative memory. *Psychol. Sci.* 17, 891–898

32 Sterpenich, V. *et al.* (2009) Sleep promotes the neural reorganization of remote emotional memory. *J. Neurosci.* 29, 5143–5152

33 Wilhelm, I. *et al.* (2011) Sleep selectively enhances memory expected to be of future relevance. *J. Neurosci.* 31, 1563–1569

34 Fischer, S. and Born, J. (2009) Anticipated reward enhances offline learning during sleep. *J. Exp. Psychol. Learn. Mem. Cogn.* 35, 1586–1593

35 Rauchs, G. *et al.* (2011) Sleep contributes to the strengthening of some memories over others, depending on hippocampal activity at learning. *J. Neurosci.* 31, 2563–2568

36 Saletin, J.M. *et al.* (2011) The role of sleep in directed forgetting and remembering of human memories. *Cereb. Cortex* 21, 2534–2541

37 Mollon, J.D. (1998) *Acquisition and processing of information during states of REM sleep and slow-wave sleep*, U.S. Army Research Institute for the Behavioral and Social Sciences (http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA341361)

38 Hars, B. *et al.* (1985) Improvement of learning by cueing during postlearning paradoxical sleep. *Behav. Brain Res.* 18, 241–250

39 Hars, B. and Hennevin, E. (1987) Impairment of learning by cueing during postlearning slow-wave sleep in rats. *Neurosci. Lett.* 79, 290–294

40 Smith, C. and Weeden, K. (1990) Post training REMs coincident auditory stimulation enhances memory in humans. *Psychiatr. J. Univ. Ott.* 15, 85–90

41 Guerrien, A. *et al.* (1989) Enhancement of memory by auditory stimulation during postlearning REM sleep in humans. *Physiol. Behav.* 45, 947–950

42 Tilley, A.J. (1979) Sleep learning during stage 2 and REM sleep. *Biol. Psychol.* 9, 155–161

43 Emmons, W.H. and Simon, C.W. (1956) The non-recall of material presented during sleep. *Am. J. Psychol.* 69, 76–81

44 Rasch, B. *et al.* (2007) Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 315, 1426–1429

45 Rudoy, J.D. *et al.* (2009) Strengthening individual memories by reactivating them during sleep. *Science* 326, 1079

46 Donohue, K. and Spencer, R.M.C. (2011) Continuous re-exposure to environmental sound cues during sleep does not improve memory for semantically unrelated word pairs. *J. Cogn. Educ. Psychol.* 10, 161–177

47 Antony, J.W. *et al.* (2012) Cued memory reactivation during sleep influences skill learning. *Nat. Neurosci.* 15, 1114–1116

48 Diekelmann, S. *et al.* (2011) Labile or stable: opposing consequences for memory when reactivated during waking and sleep. *Nat. Neurosci.* 14, 381–386

49 Oudiette, D. *et al.* (2013) The role of memory reactivation during wakefulness and sleep in determining which memories endure. *J. Neurosci*. (in press)

50 Bendor, D. and Wilson, M.A. (2012) Biasing the content of hippocampal replay during sleep. *Nat. Neurosci.* 15, 1439–1444

51 Bridge, D.J. and Paller, K.A. (2012) Neural correlates of reactivation and retrieval-induced distortion. *J. Neurosci.* 32, 12144–12151

52 Diekelmann, S. *et al.* (2012) Offline consolidation of memory varies with time in slow wave sleep and can be accelerated by cuing memory reactivations. *Neurobiol. Learn. Mem.* 98, 103–111

53 van Dongen, E.V. *et al.* (2012) Memory stabilization with targeted reactivation during human slow-wave sleep. *Proc. Natl. Acad. Sci. U.S.A.* 109, 10575–10580

54 Arzi, A. *et al.* (2012) Humans can learn new information during sleep. *Nat. Neurosci.* 15, 1460–1465

55 Paller, K.A. and Voss, J.L. (2004) Memory reactivation and consolidation during sleep. *Learn. Mem.* 11, 664–670

56 Cartwright, R.D. (2010) *The Twenty-Four Hour Mind: The Role of Sleep and Dreaming in our Emotonal Lives*, Oxford University Press

57 Carskadon, M.A. and Herz, R.S. (2004) Minimal olfactory perception during sleep: why odor alarms will not work for humans. *Sleep* 27, 402–405

58 Amo, L. *et al.* (2011) Sleeping birds do not respond to predator odour. *PLoS ONE* 6, e27576

59 Arzi, A. *et al.* (2010) The influence of odorants on respiratory patterns in sleep. *Chem. Senses* 35, 31–40

60 Stuck, B.A. *et al.* (2007) Arousal responses to olfactory or trigeminal stimulation during sleep. *Sleep* 30, 506–510

61 Goel, N. *et al.* (2005) An olfactory stimulus modifies nighttime sleep in young men and women. *Chronobiol. Int.* 22, 889–904

62 Stuck, B.A. *et al.* (2006) Chemosensory event-related potentials during sleep – a pilot study. *Neurosci. Lett.* 406, 222–226

63 Seelke, A.M. and Blumberg, M.S. (2004) Sniffing in infant rats during sleep and wakefulness. *Behav. Neurosci.* 118, 267–273

64 Busby, K.A. *et al.* (1994) Ontogenetic variations in auditory arousal threshold during sleep. *Psychophysiology* 31, 182–188

65 Williams, H.L. *et al.* (1964) Responses to auditory stimulation, sleep loss and the EEG stages of sleep. *Electroencephalogr. Clin. Neurophysiol.* 16, 269–279

66 Oswald, I. *et al.* (1960) Discriminative responses to stimulation during human sleep. *Brain* 83, 440–453

67 Campbell, K.B. and Bartoli, E.A. (1986) Human auditory evoked potentials during natural sleep: the early components. *Electroencephalogr. Clin. Neurophysiol.* 65, 142–149

68 Bastuji, H. and Garcia-Larrea, L. (1999) Evoked potentials as a tool for the investigation of human sleep. *Sleep Med. Rev.* 3, 23–45

69 Colrain, I.M. and Campbell, K.B. (2007) The use of evoked potentials in sleep research. *Sleep Med. Rev.* 11, 277–293

70 Issa, E.B. and Wang, X. (2008) Sensory responses during sleep in primate primary and secondary auditory cortex. *J. Neurosci.* 28, 14467–14480

71 Issa, E.B. and Wang, X. (2011) Altered neural responses to sounds in primate primary auditory cortex during slow-wave sleep. *J. Neurosci.* 31, 2965–2973

72 Portas, C.M. *et al.* (2000) Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. *Neuron* 28, 991–999

73 Czisch, M. *et al.* (2002) Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. *Neuroimage* 16, 251–258

74 Dang-Vu, T.T. *et al.* (2011) Interplay between spontaneous and induced brain activity during human non-rapid eye movement sleep. *Proc. Natl. Acad. Sci. U.S.A.* 108, 15438–15443

75 Schabus, M. *et al.* (2012) The fate of incoming stimuli during NREM Sleep is determined by spindles and the phase of the slow oscillation. *Front. Neurol.* 3, 40

76 Massimini, M. *et al.* (2007) Triggering sleep slow waves by transcranial magnetic stimulation. *Proc. Natl. Acad. Sci. U.S.A.* 104, 8496–8501

77 Marshall, L. *et al.* (2006) Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613

78 Ngo, H.V. *et al.* (2013) Induction of slow oscillations by rhythmic acoustic stimulation. *J. Sleep Res.* 22, 22–31

79 Aeschbach, D. *et al.* (2008) A role for non-rapid-eye-movement sleep homeostasis in perceptual learning. *J. Neurosci.* 28, 2766–2772

80 Landsness, E.C. *et al.* (2009) Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep* 32, 1273–1284

81 Huber, R. *et al.* (2006) Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat. Neurosci.* 9, 1169–1176

82 Huber, R. *et al.* (2004) Local sleep and learning. *Nature* 430, 78–81

83 Huber, R. *et al.* (2008) Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *J. Neurosci.* 28, 7911–7918

84 Tononi, G. and Cirelli, C. (2006) Sleep function and synaptic homeostasis. *Sleep Med. Rev.* 10, 49–62

85 Cartwright, R.D. *et al.* (1969) Effect of an erotic movie on the sleep and dreams of young men. *Arch. Gen. Psychiatry* 20, 262–271

86 Dement, W. and Wolpert, E.A. (1958) The relation of eye movements, body motility, and external stimuli to dream content. *J. Exp. Psychol.* 55, 543–553

87 Fosse, M.J. *et al.* (2003) Dreaming and episodic memory: a functional dissociation? *J. Cogn. Neurosci.* 15, 1–9

88 Roffwarg, H.P. *et al.* (1978) The effects of sustained alterations of waking visual input on dream content. In *The mind in sleep* (Arkis, A.M. *et al.*, eds), pp. 295–349, Erlbaum Associates

89 Stickgold, R. *et al.* (2000) Replaying the game: hypnagogic images in normals and amnesics. *Science* 290, 350–353

90 Wamsley, E.J. *et al.* (2010) Cognitive replay of visuomotor learning at sleep onset: temporal dynamics and relationship to task performance. *Sleep* 33, 59–68

91 Wegner, D.M. *et al.* (2004) Dream rebound: the return of suppressed thoughts in dreams. *Psychol. Sci.* 15, 232–236

92 Leslie, K. and Ogilvie, R. (1996) Vestibular dreams: the effect of rocking on dream mentation. *Dreaming* 6, 1–16

93 Nielsen, T.A. *et al.* (1993) Pain in dreams. *Sleep* 16, 490–498

94 Koulack, D. (1969) Effects of somatosensory stimulation on dream content. *Arch. Gen. Psychiatry* 20, 718–725

95 Schredl, M. *et al.* (2009) Information processing during sleep: the effect of olfactory stimuli on dream content and dream emotions. *J. Sleep Res.* 18, 285–290

96 Wamsley, E.J. and Antrobus, J.S. (2009) The expression of trace conditioning during non-REM sleep and its relation to subjective experience. *Neurobiol. Learn. Mem.* 92, 283–291

97 Wamsley, E.J. *et al.* (2010) Dreaming of a learning task is associated with enhanced sleep-dependent memory consolidation. *Curr. Biol.* 20, 850–855

98 Ritter, S.M. *et al.* (2012) Good morning creativity: task reactivation during sleep enhances beneficial effect of sleep on creative performance. *J. Sleep Res.* 21, 643–647

99 Westerberg, C.E. *et al.* (2012) Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 18, 490–500