Current Directions in Psychological Science
2017, Vol. 26(6) 532–537

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DOI: 10.1177/0963721417716928
www.psychologicalscience.org/CDPS

Sleeping in a Brave New World: Opportunities for Improving Learning and Clinical Outcomes Through Targeted Memory Reactivation

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Abstract

Neuroscientific insights into learning and memory have mostly concerned input and output, but intervening processing during the time between acquisition and retrieval is also critical. Indeed, intervening memory reactivation may regulate memory longevity, and a growing body of evidence implicates sleep in changing memory storage. For example, subtle auditory stimulation can be used experimentally to selectively encourage memory reactivation during sleep, which thereby improves learning. Much remains to be elucidated about how learning depends on sleep. Nevertheless, this methodology for modifying memory storage during sleep offers new opportunities for reinforcing learning to enhance clinical outcomes in conjunction with therapies engaged during waking. A variety of such possibilities must now be carefully investigated. Likewise, brain rhythms can be entrained to enhance sleep functions, facilitating further progress in understanding the neurophysiological basis of memory processing during sleep. Ultimately, empirical evidence may reveal the extent to which the way we behave when awake is a function of what our brains do when we are asleep. Through such research efforts, an advanced understanding of memory and sleep may allow us to both make better use of our time asleep and take steps toward better health.

Keywords

learning, memory reactivation, sleep, rehabilitation, psychotherapy

> O brave new world,
> That has such people in't!
>
> —Miranda in William Shakespeare's *The Tempest*, Act 5, Scene 1

Learning Each Day

Countless memories are stored in the brain during the course of just a single day. At the end of the day, we can usually remember a sequence of events and actions from that day, plus various places, people, conversations, thoughts, and emotions experienced. As each experience enters the mind, it leaves a trace in the brain.

Despite the tremendous amount of learning accomplished each day, most memories are forgotten. Yet some are stabilized, and a select few endure indefinitely. What causes some memories to escape this pervasive forgetting?

In a word: practice. Practice is the key to remembering. The memories most likely to endure are those that are well rehearsed. And it seems that we must be awake when we memorize information, develop a new skill, or rehearse knowledge or skills—but that is not the whole story. Enter sleep.

Learning and Sleep

Sleep naturally aids learning. Although learning begins when a person is awake, it is seldom or ever a one-shot fait accompli. To be effective, learning must continue. It continues when we intentionally rehearse, as in repeating the name of a person you have just met. New

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information is also rehearsed when it spontaneously comes to mind again. Although momentous events may seem to be hammered in instantaneously, a tremendous amount of rehearsal may actually underlie their strong memorability. Importantly, rehearsal can also happen when we do not realize it—while we are sleeping.

Sleep is essential. We each spend about a third of a lifetime asleep, but what the brain is doing during sleep has long remained mysterious. Medical diagnosis naturally underemphasizes the relevance of sleep. Yet there is a growing realization that poor sleep has insidious effects on health and well-being. By taking on board the essential role played by sleep in supporting learning, we elevate the importance of sleep yet further.

When specific memories stored in brain networks come to be active during sleep, this reactivation helps establish enduring memory storage. Various lines of evidence have implicated sleep in memory stability (e.g., Axmacher & Rasch, 2017; Diekelmann & Born, 2010; Paller & Voss, 2004), but the experimental strategy of *targeted memory reactivation* (TMR) has provided the most direct evidence (see Schouten, Pereira, Tops, & Louzada, 2017, for a review). Rasch, Büchel, Gais, and Born (2007) showed that an odorant presented during sleep enhanced learning of spatial locations. TMR can also be accomplished by presenting low-intensity auditory cues during slow-wave sleep (SWS) to promote memory rehearsal without awakening (Oudiette & Paller, 2013). As discussed below, TMR allows us to modify specific memories. Before delving into that topic, we should consider what is required for effective learning.

First, new information must be understood in the context of other knowledge. At the same time, new learning should not corrupt the storage of other useful information. Memory researchers take *consolidation* to be the process whereby new information is selectively retained and assimilated (Paller, 2009). For new facts and events (known as *declarative memories*), consolidation depends on interactions among sets of networks in the cerebral cortex and hippocampus. Through these interactions, consolidation can entail changes in how information is represented within cortical networks (Moscovitch, Winocur, Cabeza, & Nadel, 2016). For other types of memory, including skills, sleep-dependent consolidation proceeds in other ways involving different sets of brain areas.

Retrieving recently acquired information often depends on activating associations between previously learned knowledge and the new information, such that these associations constitute retrieval routes. Retrieval becomes easier when retrieval routes proliferate. Put another way, memory storage is strengthened when new information is integrated within existing knowledge networks. Sleep may play an essential role in this sort of consolidation processing.

By taking new information into account, we can learn to adjust to environmental demands to achieve our goals. In this way, consolidation can aid human flourishing. Yet consolidation is somewhat hidden; we know when we intentionally rehearse information we wish to retain, but we cannot keep tabs on the operation of sleep-dependent consolidation.

Consider that during a typical day we are exposed to both relatively important information (such as the names of new acquaintances) and relatively unimportant information (such as advertising for unwanted products). That night we might engage in suboptimal sleep-dependent consolidation if we rehearse information we would prefer to forget instead of information we wish to retain. An intriguing research question is whether TMR could work outside the laboratory environment to bias rehearsal during sleep toward the most valuable information.

Despite attempts to control sleep with pharmacological and behavioral therapies, only coarse control has been possible. On the other hand, precise and targeted control may be achieved via stimuli that guide the sleeping brain on a moment-to-moment basis. Research on these possibilities must proceed carefully, especially given the importance of sleep for restoring mental and physical capabilities generally.

Targeted Memory Reactivation for Declarative Memories

Empirical findings at the root of such novel applications demonstrated that subtle sounds presented during sleep can impact memory processing so as to strengthen specific memories (Oudiette & Paller, 2013). Although auditory approaches are emphasized here, stimulation with other modalities can also be valuable. The general form of these experiments is threefold. First, learning takes place using memory tasks including an auditory component. Second, subjects sleep with electroencephalographic (EEG) monitoring of brain activity, such that sounds can be presented during SWS defined by standard criteria. Sounds from the learning session can be presented very quietly, avoiding sleep disruption or arousal, as evidenced by EEG signals. The sounds function as reminders of prior learning, prompting memory reactivation. The third and final step is memory testing after waking, providing the critical behavioral results to substantiate selective memory improvement.

TMR is effective with spatial learning, as in memorizing where objects appear on a grid, as recall can be selectively improved using sounds linked with learning and presented again during SWS (Rudoy, Voss, Westerberg,

& Paller, 2009). Learning prior to sleep must reach a certain level of accuracy for best TMR efficacy (Creery, Oudiette, Antony, & Paller, 2015). Consolidation during sleep likely involves a cascade of neurophysiological events that includes slow waves, thalamocortical sleep spindles, and hippocampal sharp-wave ripples (Staresina et al., 2015). Further research is needed to reveal precisely how cross-frequency coupling and other aspects of sleep physiology support the neocortical-hippocampal interactions thought to underlie declarative memory consolidation.

Memory consolidation is a normal consequence of sleep. TMR, with low-intensity auditory cues to prompt rehearsal without awakening, can build on these consolidation mechanisms and allow specific memories to be reactivated during sleep. TMR may thus provide a direct and specific way to promote neuroplasticity during sleep, even beyond declarative memory.

TMR for Skills and Habits

Memory researchers distinguish declarative memory from several other types of memory that are typically not accompanied by the experience of remembering. With skills and habits, for example, we demonstrate our knowledge when engaging in some activity but may not have any awareness that our actions have been influenced by prior experiences.

In our first study of TMR for skill learning (Antony, Gobel, O'Hare, Reber, & Paller, 2012), we taught volunteers to perform two melodies. Then a nap with TMR ensued, during which we played one of the melodies repeatedly. After sleep, we found a selective advantage for the melody presented during sleep (Fig. 1, left panel). From these findings, we concluded that TMR can activate brain networks instrumental for learning a specific skill so as to improve performance.

We also used TMR following a short session of counterstereotype training (Hu et al., 2015), which produces a temporary reduction in implicit social bias. This bias-reduction training was reactivated and enhanced during sleep, in comparison with bias-reduction training not reactivated during sleep (Fig. 1, right panel). More generally, learning to enhance good habits (e.g., gratitude and compassion) might also be enhanced if learning were followed by memory reactivation during sleep.

The proposed clinical application of TMR is premised on the idea that current therapies for psychiatric and neurological disorders often require the patient to learn to change behavior or acquire new skills. This therapy-based learning may involve a combination of memory systems, often including skill learning; one might attempt to replace a detrimental habit with an advantageous one.

TMR in a Clinical Context

The extent to which a therapy is successful is often a function of the degree to which learning progresses. For example, physical therapy might require repeated execution of a new motor task so as to strengthen certain motor pathways in the brain. Therapies for anxiety disorders require learning to habituate to previously threatening experiences or thoughts. Therapies for depression may attempt to alter patterns of dysfunctional thinking.

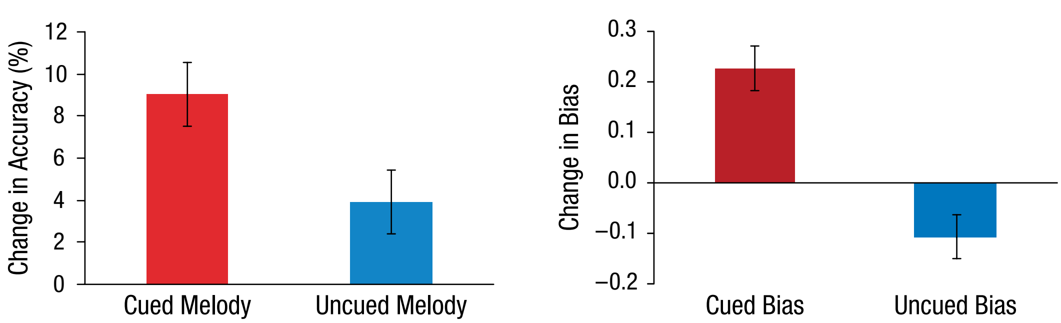

Fig. 1. In the experiment reported by Antony, Gobel, O'Hare, Reber, & Paller (2012; results shown in the left panel), people learned to play two 12-note melodies on a keyboard in sync with moving circles. To produce the correct notes, participants had to hit the correct key at precisely the correct time (as in the *Guitar Hero* video game). After training, average performance accuracy was 77%. Following a nap when one melody was played during slow-wave sleep, participants showed a greater performance improvement for that melody compared with the uncued melody. In the experiment reported by Hu and colleagues (2015; results shown in the right panel), counterstereotype training produced a reduction in implicit social bias for race or gender as measured using the Implicit Association Test. After this training, standardized implicit-bias scores were reduced by an average of 0.224. Then, following a nap when the sound associated with one type of bias training was played during slow-wave sleep, participants showed a greater change for the cued bias compared with the other bias. A positive change score indicates a further reduction in bias from the level reached after training, whereas a negative change score indicates a return in the direction of the typical racial or gender bias.

What if these therapies could proceed more rapidly and be made more effective by taking advantage of sleep time to reinforce daytime learning sessions?

Adapting TMR methods from basic research is straightforward. Sounds can readily be added to standard therapies and to sleep. When therapeutic improvement fundamentally involves learning, we expect TMR-assisted treatments to yield better outcomes in comparison with current treatment options alone. Patients could use TMR with subtle auditory stimulation controlled by a laptop or smartphone wirelessly connected for monitoring sleep physiology. Technological developments are likely to make monitoring sleep progressively more feasible in the home environment. Studies conducted in the sleep lab would also be advantageous because full polysomnographic recordings could be included and full control exerted over auditory stimulation and environmental factors. Of course, TMR could have downsides, such as decrements in the restorative benefits of sleep, but by remaining alert for problems, we could hopefully make adjustments to minimize side effects if any are detected.

Speeding recovery after neurological injury

Neuroplasticity can contribute to recovery following stroke or other brain insults. Repeated physical rehab sessions can improve motor networks, and likewise for language networks with speech rehab. Can learning to restructure these networks be facilitated by TMR-assisted memory consolidation during sleep?

For example, a set of weekly therapy sessions might focus on the viability of neural pathways through their repeated activation in a steadily more refined manner. Standard types of therapy along these lines can help with motor problems such as overcoming the typical loss of independent joint control in a paretic arm. Gradual neuroplasticity via therapy also aligns with the literature on sleep consolidation and motor learning.

A therapy protocol could be modified such that distinctive auditory signals accompany desired movements. In this way (as in Antony et al., 2012), sounds can be tightly associated with learning to properly engage motor networks in the brain. TMR could then reactivate those networks during sleep and potentially quicken the reacquisition of independent joint control, so that the patient regains motor function more quickly.

Analogous sorts of recovery should be sought with cognitive rehab, such as to regain speech production after stroke. Contemporary aphasia rehab procedures could be adapted to determine if TMR could promote more effective recovery. The two steps would be to add (a) distinctive sounds to the cognitive challenges applied during rehab and (b) a nocturnal intervention with TMR. This strategy could also be adapted for behavioral therapies to treat other disorders.

Reversing maladaptive learning

Disorders that stem from maladaptive learning are often treated using learning protocols, essentially replacing bad habits with good ones. In exposure therapy for phobia, for instance, therapy sessions might focus on replacing the anxiety response with a calm response. TMR could function to enhance therapy-based learning in these situations. Supporting the feasibility of this approach, sleep manipulations have been used to attenuate conditioned fear in lab studies (e.g., Hauner, Howard, Zelano, & Gottfried, 2013), although whether this particular approach would be useful more generally is currently unknown.

In exposure therapy, a safe environment is maintained while carefully increasing exposure to the fear-provoking stimulus. Patients who initially suffer a debilitating fear are gradually led by a skilled therapist to calmly deal with the object of fear and overcome their disability. This basic therapy can produce a lasting cure in cases of spider phobia (Hauner, Mineka, Voss, & Paller, 2012), but typically patients with other phobias do not so readily lose their fears. Compliance can also be a problem, because patients may wish to avoid revisiting traumatic experiences.

TMR may offer a way to supplement and improve on contemporary therapeutic practices. Therapy protocols can be modified by repeatedly pairing a distinctive tone sequence with an intervention, to enable later TMR. For example, the tones can provoke rehearsal of the calm therapeutic experience. As in our laboratory-based memory tasks, the goal is to speed the course of learning. If patients can learn more rapidly, they might more effectively overcome troublesome responses.

Other possibilities for TMR should be investigated with disorders of depression, anxiety, obsessive-compulsive disorder, and posttraumatic stress disorder. Nightmares are already common in some of these patients, so strategies must take care to avoid provoking further distress.

In postpartum depression, new mothers can experience distressing obsessional thoughts about the baby. Cognitive-behavioral therapy for such problems could be reinforced during sleep with TMR. In addition, parental sleep can be suboptimal because of hypervigilance for sounds of the infant, such that abnormal sleep could be part of the etiology. One possible sleep-based therapy could involve a “safe sound” associated with the infant being okay.

Finally, contemporary treatments for addictive behaviors might be improved. For example, studies could determine whether TMR would help individuals with eating disorders learn to develop healthier eating habits, and likewise for drug or gambling addiction. Standard treatments for smoking cessation might likewise be improved (sleep conditioning could also be a useful strategy; Arzi et al., 2014).

Habits are like skills that can be learned or unlearned by modifying particular brain networks. Great effort is often required when habits are ingrained. Nevertheless, a combination of efforts in waking and in sleep might be more effective than waking efforts alone.

Sound stimulation and sleep physiology

Sleep problems are widespread. Good-quality sleep is essential, which requires good sleep hygiene. We lay down each night wishing to drop off quickly and sleep soundly. When this does not go well, fatigue and other problems result. Sleep deteriorates with aging and may contribute to age-related memory impairment (Mander et al., 2013; Westerberg et al., 2012). New approaches that combine sensory stimulation with EEG monitoring should be examined to see if it is possible to perpetuate restful and effective sleep.

Auditory stimulation can entrain brain rhythms and might thus enhance sleep functions. Oscillating electrical stimulation at slow-wave frequencies facilitates both SWS and memory (Marshall, Mölle, Hallschmid, & Born, 2004; Westerberg et al., 2015). Auditory stimulation likewise produces memory benefits (Ngo, Martinetz, Born, & Mölle, 2013; Ong et al., 2016). Sleep spindles can also be entrained (Antony & Paller, 2017). Comprehensive brain-entrainment methods may ultimately be devised to orchestrate sleep physiology and help individuals to progress through sleep stages in an optimal way.

The combination of entraining brain rhythms and engaging memory reactivation may multiply potential benefits. Conditioning with auditory sounds might also be used to prevent an individual from engaging in maladaptive actions during sleep or to avoid nightmares (e.g., treating bruxism with a sound repeatedly paired with the command to release jaw-clenching during waking). Many such innovative ways to improve sleep are now calling out for new research.

Sleeping in a Brave New World?

Would the picture sketched here allow for mind control without an individual's knowledge or consent? One might imagine unethical uses of TMR—a hotel owner, for example, could surreptitiously play pro-hotel messages to hotel guests while they sleep. Alternatively, sociopaths in prison could be rewired to behave nicely, and political prisoners rewired to behave in accordance with the wishes of a totalitarian dictator.

Huxley (1932) portrayed a world in which the state controlled each individual, starting at an early age through what he called *hypnopædia*, or sleep teaching. People had very little choice in the matter and were bred to assume their assigned roles in society, high or low. Contrary to the procedure in hypnopædia, TMR is based on reinforcing training during waking. Participants are aware of what they are learning, and they have the opportunity to reject the training. Nevertheless, we should observe caution given that scenarios might be contrived to apply TMR in a coercive manner, without an individual's consent.

In conclusion, neuroscientific findings on memory processing during sleep have opened up a new world of innovative possibilities for guiding the sleeping brain in adaptive ways. Here, I have emphasized the potential for various therapies to be improved by supplementing standard procedures with an additional sleep-based component. If neural mechanisms of memory can be harnessed during sleep to improve clinical treatment, we may also be able to increase our understanding of the fundamental role of neuroplasticity in promoting well-being.

Recommended Reading

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Acknowledgments

I am grateful for ongoing interactions with many students and colleagues, and for input from three anonymous referees. My work has also been influenced by the valuable research of many other investigators. I apologize that only a small portion of that research could be cited here.

Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

Funding

Research was supported by the National Science Foundation (BCS-1025697, BCS-1461088, and BCS-1533511), the BrightFocus Foundation (A2011362), the Alzheimer's Association (HAT-08-86763), and the Mind Science Foundation.

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