Journal of Neuroscience Methods 316 (2019) 125–136

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Stimulating the sleeping brain: Current approaches to modulating memory-related sleep physiology

Nicola Cellini[a,*], Sara C. Mednick[b]

[a] Department of General Psychology, University of Padova, Padova, Italy
[b] Department of Cognitive Sciences, University of California, Irvine, United States

ARTICLE INFO

Keywords:
Closed-loop system
Memory consolidation
Non-Invasive brain stimulation
Pharmacological intervention
Sleep
Slow oscillations

ABSTRACT

Background: One of the most audacious proposals throughout the history of psychology was the potential ability to learn while we sleep. The idea penetrated culture via sci-fi movies and inspired the invention of devices that claimed to teach foreign languages, facts, and even quit smoking by simply listening to audiocassettes or other devices during sleep. However, the promises from this endeavor didn't stand up to experimental scrutiny, and the dream was shunned from the scientific community. Despite the historic evidence that the sleeping brain cannot learn new complex information (i.e., words, images, facts), a new wave of current interventions are demonstrating that sleep can be manipulated to strengthen recent memories.

New method: Several recent approaches have been developed that play with the sleeping brain in order to modify ongoing memory processing. Here, we provide an overview of the available techniques to non-invasively modulate memory-related sleep physiology, including sensory, vestibular and electrical stimulation, as well as pharmacological approaches.

Results: N/A.

Comparison with existing methods: N/A.

Conclusions: Although the results are encouraging, suggesting that in general the sleeping brain may be optimized for better memory performance, the road to bring these techniques in free-living conditions is paved with unanswered questions and technical challenges that need to be carefully addressed.

1. Introduction

While asleep, our brains not only rest, but also reprocess and reorganize the information we acquired throughout the day (Conte and Ficca, 2013). Compelling evidence has recently suggested that sleep promotes memory consolidation, the process by which labile information becomes stronger, more efficient, and more resistant to interference (Rasch and Born, 2013; Diekelmann and Born, 2010) (Whitehurst et al., 2016). While the role of sleep for memory has been recognized since the pioneering study by Jenkins and Dallenbach (1924), it is only in the last two decades that researchers have begun to use interventions to reveal the mechanisms underlying the observed effects of sleep-related memory processes.

1.1. Sleep and memory consolidation: theoretical models

An influential and enduring model of memory, entitled the complementary learning system model (CLS) (Norman et al., 2005; O'Reilly et al., 2014), proposed that during wakefulness information is initially encoded in parallel in two different memory systems: in the hippocampus, where memories are stored at a faster rate in a pattern-separated fashion, and in cortical networks, where they are stored at a slower rate in an overlapping and distributed manner across several memory networks (O'Reilly et al., 2014). During subsequent sleep periods, specifically non-rapid eye movement sleep (NREM, composed by stage N1, N2, and N3, the latter also known as slow-wave sleep, SWS), the pieces of information acquired during wake are repetitively re-activated in both the hippocampus and the cortex. These reactivations, through a constant dialogue between the hippocampus and the neocortex (Buzsáki, 1989), mediate the redistribution of information in cortical areas, a process also known as "system consolidation" (Diekelmann and Born, 2010). Cortical connections are also strengthened and stabilized via synaptic consolidation and eventually integrated with pre-existing knowledge, making the encoded event less susceptible to interference (Rasch and Born, 2013; Mednick et al., 2011). Once stabilized, the recent memory can be integrated within

* Corresponding author at: Department of General Psychology, University of Padova, Via Venezia 8, 35131 Padova, Italy.
E-mail address: nicola.cellini@unipd.it (N. Cellini).

https://doi.org/10.1016/j.jneumeth.2018.11.011
Received 22 June 2018; Received in revised form 25 October 2018; Accepted 14 November 2018
Available online 16 November 2018
0165-0270/

semantic networks during subsequent sleep states [e.g., rapid eye movement (REM) sleep and the transition to REM]. Successful integration likely requires a multi-step process to first weaken or loosen existing connections, followed by reconsolidation of the old memories with the newly incorporated information (Poe, 2017; Li et al., 2017; Sara, 2017).

Several models have been put forth attempting to illustrate the dynamic relationship between key sleep features and the hippocampal-neocortical dialogue characteristic of systems consolidation. According to the active system consolidation model (Diekelmann and Born, 2010; Born and Wilhelm, 2012), a critical aspect of consolidation is the temporal coupling of neural oscillations from several memory-related brain areas, including cortical slow oscillations (SO; large amplitude oscillations of 0.5–1 Hz), thalamic sleep spindles (i.e., short oscillatory bursts of 9–16 Hz originated in the reticular thalamus), and hippocampal sharp-wave ripples (SWR; transient and fast excitatory oscillations of about 200 Hz originating in the hippocampus). Indeed, SOs appear to provide a temporal framework whereby the depolarizing up phases of SOs promote the reactivation of information in hippocampal networks in parallel with sleep spindles, allowing these oscillations to reach the cortical networks at about the same time and in the depolarizing up-state (Wei et al., 2017; Staresina et al., 2015; Mak-McCully et al., 2017; Maingret et al., 2016). Of note, recent studies have suggested that sleep spindles can be differentiated into slow (9–12 Hz) and fast (12–16 Hz) spindles, with the latter reflecting thalamo-cortical communication and directly associated with memory reorganization during sleep (Mölle et al., 2011). A different representation has been proposed by the Synaptic Homeostasis Hypothesis (SHY), which proposes that waking experience leads to an increase in synaptic potentiation across the day, and that NREM SOs drive the process of downscaling these synaptic weights while leaving some salient connections intact (Tononi and Cirelli, 2003, 2014). This is a compelling prediction given that decreased potentiation is required to maintain balance in a biological system, and the selective reweighting may explain to some degree the process by which some memories are retained while others are forgotten. However, the model does little to incorporate the vast amount of evidence from human and animal studies demonstrating the importance of system-level communication and the critical nature of sleep spindles and SWR in this process. A third model by Genzel and colleagues (2014) has valiantly worked to synthesize aspects of both active systems and SHY by suggesting that both systems consolidation and synaptic downscaling can occur through sequential sleep stages. In this model, Light Stage 2 sleep (N2) engages global thalamocortical communication via SWR, spindles, and K-complexes, while deep SWS promotes local weakening of synaptic units. Regardless of the model, the building blocks of sleep-dependent consolidation, SOs, sleep spindles, and SWR, can be agreed upon as having critical roles in the process and therefore these sleep features have become key targets of non-invasive interventions to improve sleep-dependent memory processes. Although these elegant models specifically pertain to hippocampal-dependent declarative memory networks, they also help explain, to a certain degree, findings from emotional (Genzel et al., 2015; Tempesta et al., 2017) and procedural memory domains, as well (see for example Vahdat et al., 2017; Maquet et al., 2000; Huber et al., 2004; Fogel et al., 2017; Debas et al., 2014).

1.2. Learning while we are asleep

One of the most audacious proposals throughout the history of psychology was the potential ability to learn while we sleep. The idea penetrated culture via sci-fi movies and inspired the invention of devices that claimed to teach foreign languages, facts, and even quit smoking by simply listening to audiocassettes or other devices during sleep. However, as demonstrated 60 years ago by Simon and Emmons (1956), humans cannot learn complex facts during sleep, and this dream was quickly discarded by the scientific community. Although the sleeping brain is unable to *acquire new complex information* (i.e., words, images, facts, but see (Arzi et al., 2012) for learning new associations during sleep), we now know that it can be manipulated to *strengthen the memory of recently acquired information.* In recent years several approaches have been developed to intervene on the sleeping brain in order to modify the ongoing memory processing. Here, we provide an overview of the available techniques to modulate memory-related sleep physiology, including sensory, vestibular and electrical stimulation, as well as pharmacological approaches. The current review is not meant to be an exhaustive literature search but to offer a general summary of possible interventions that may be used to stimulate the sleeping brain in order to shape memory consolidation.

2. Sensory stimulation

The sleeping brain is not indifferent to external sensory information, which may modulate memory-related sleep physiology. Indeed, already in 1939, Davis and colleagues observed that the presentation of acoustic tones during sleep can elicit a SO/K-complex followed by slow (8 Hz) or fast (14 Hz) spindles. Also, olfactory stimulation during sleep modulates sleep physiology. Odor presentation (e.g., lavender) during NREM sleep induces greater SWS (Goel et al., 2005), and increases delta (0.5–4 Hz) (Perl et al., 2016; Arzi et al., 2014) and slow spindle (9–12 Hz) power (Perl et al., 2016). Interestingly, olfactory stimuli can be used to create new associations during sleep (Arzi et al., 2012), which can impact behaviors such as smoking habits (Arzi et al., 2014).

Capitalizing on the ability of the sleeping brain to process external sensory information, Rasch and colleagues (2007) made a seminal discovery: the sleeping brain can be manipulated to strengthen the memory of specific, recently acquired information. During encoding, a sensory cue (i.e., the scent of a rose) was paired with the target information to learn (i.e., the position of two identical pairs in a grid of cards, as in the game “Memory”) and then the contextual cue (the scent) was re-presented during sleep. They observed that the odor stimulation during SWS, but not during wakefulness or during REM sleep, was able to enhance the memory for the pair of cards at morning recall. Moreover, the olfactory stimulation induced greater hippocampal activity during sleep compared to sleeping without the odor or with an odorless “vehicle” stimulation. This breakthrough study, which was the first to show that memory-related sleep physiology could be modified during sleep, had a major impact on the sleep field, leading to the development of new research paradigms, including targeted memory reactivation (TMR), rhythmic stimulation and closed-loop stimulation during sleep (described in the following paragraphs).

2.1. Stimulating with meaningful sensory cues: targeted memory reactivation (TMR)

Targeted memory reactivation (TMR) is a well-established paradigm that employs sensory stimulation to modulate memory consolidation during sleep (Cellini and Capuozzo, 2018). It consists of matching a sensory *cue* (e.g., an odor or a sound) with a target (e.g., a picture, a word) during wakefulness, and then re-presenting the *cue* alone during sleep (Fig. 1). This process facilitates the consolidation of the targeted information. Studies have shown that TMR can improve visual (Rasch et al., 2007) and verbal memories (Schreiner and Rasch, 2014b), enhance motor skills (Antony et al., 2012) and fear extinction (Hauner et al., 2013), and even modify implicit social biases (Hu et al., 2015). The idea behind TMR is that the sensory cue can induce a reactivation of the cued-target information, prioritizing its consolidation compared to uncued stimuli (i.e., encoded items in which the cue was not re-presented during sleep).

TMR can be performed with different types of sensory stimuli. As mentioned in the previous paragraph, Rasch et al. (2007) were able to enhance visuospatial memories (object-location task) using an olfactory stimulus (i.e., the scent of a rose delivered via olfactometer and nasal

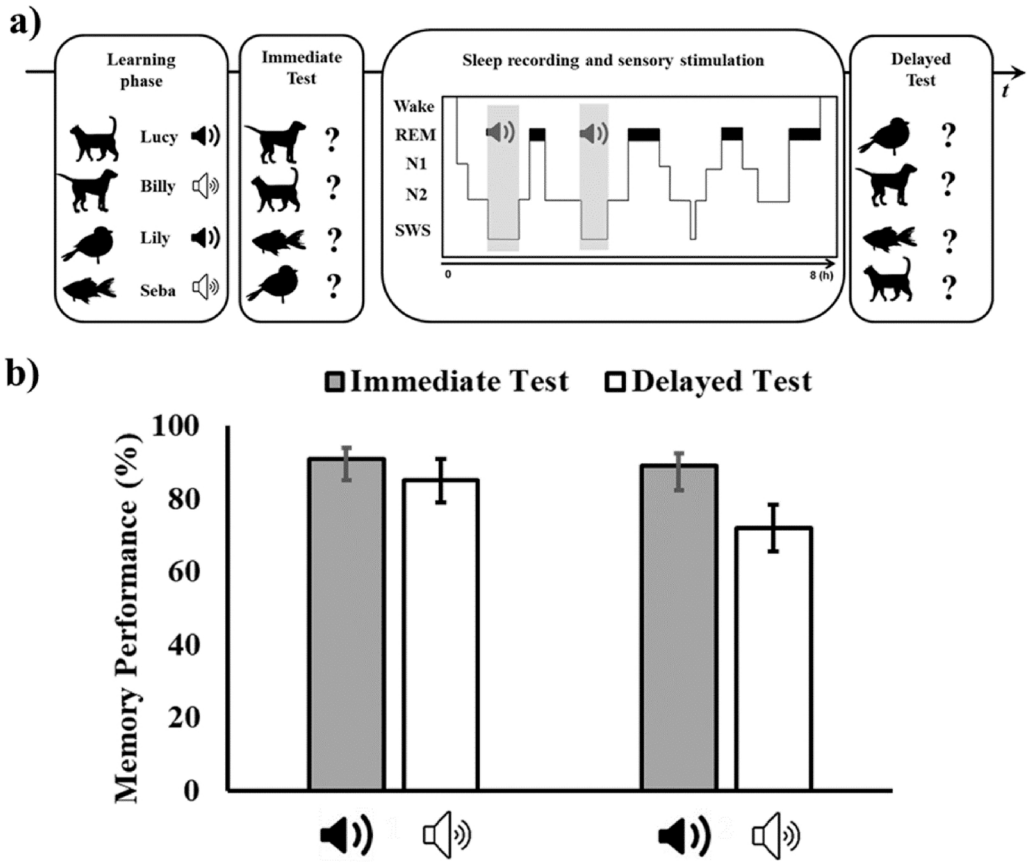

Fig. 1. Example of a targeted memory reactivation (TMR) paradigm. a) a) During the learning phase, participants are asked to encode some information (e.g., a picture-name association) which are associated with sensory cues (e.g., a specific tone). Afterward, participants are asked to perform an immediate memory test (e.g., a cued-recall test) followed by a sleep period. While participants are asleep, the sensory cues are repeatedly represented during specific sleep stages (i.e., slow wave sleep). After the awakening participants perform a delayed test. **b)** Example of a TMR result. Performance at the immediate test is similar for items that will be cued and items that will not be cued. At the delayed test, performance for the items cued during sleep is higher compared to the items not cued during sleep.

mask). In a series of experiments, they showed that the effect of stimulation was evident only when the odor was presented during SWS (in a 30-s on/30-s off sequence), and only when the odor was previously matched with the object-location to be learned. Several studies have replicated and extended these results (for recent reviews see (Cellini and Capuozzo, 2018; Schouten et al., 2017)), showing for example that the olfactory cues during SWS can induce a strong stabilization of memory traces making this information resistant to subsequent interference learning (e.g., learning new card-pair locations) (Diekelmann et al., 2011). At the physiological level, the presentation of a sensory cue during sleep increases frontal delta (1.5–4.5 Hz) and parietal fast spindle (13–15 Hz) activity (Rihm et al., 2014), which are presumed to coordinate reactivation and consolidation of declarative memories from the hippocampus to the cortical networks (Genzel et al., 2014; Rasch and Born, 2013). The beneficial effect of olfactory TMR is hypothesized to be due to the particular nature of the olfactory system, which projects directly to the hippocampus and the amygdala (Zelano and Sobel, 2005), along with its connections to the mediodorsal nucleus of the thalamus (Courtiol and Wilson, 2013). Studies using olfactory stimulation during sleep have been extended to other memory domains, showing positive effects on emotional memories and creativity skills, although findings on procedural memories and fear conditioning are less clear (Cellini and Capuozzo, 2018). These mixed results are likely due to the different paradigms used, and/or to strong individual differences, which may limit the benefits of olfactory TMR.

Building on the initial findings from Rasch et al. (2007), Rudoy et al. (2009) introduced acoustic stimulation during sleep, which allowed to overcome some of the limitations of olfactory cuing. For example, the limits of the olfactory system made it difficult to use several odors at the same time to target individual items. Also, olfactory stimuli cannot be delivered in a temporally precise fashion. Instead, acoustic stimulation can be delivered with a high temporal accuracy, and different sounds can be used in the same experiment without impairing the auditory system. Moreover, acoustic cues can be easily manipulated in order to create cues that are semantically related to individual items.

Rudoy et al. (2009) asked participants to learn the location of 50 pictures of animals/objects displayed on a computer screen. Each picture was associated with a unique and semantically related sound (e.g., a picture of a cat with a *meow*). During sleep (a 60–80 min nap), subjects were then presented with half of the auditory cues (with intensity ~38 dB SPL), which resulted in higher memory accuracy for the sleep-cued objects, compared with the non-sleep-cued objects. Other studies have replicated these findings with different types of memories (e.g., verbal, visuospatial, procedural), whereas others have failed to find a behavioral effect (reviewed in (Cellini and Capuozzo, 2018)). At the physiological level, imaging studies report that auditory cueing increased activity in hippocampal and parahippocampal cortices (van Dongen et al., 2012; Hauner et al., 2013), as well as in the occipital cortex when the stimulation was performed either in NREM (Berkers et al., 2017) or in REM sleep (Sterpenich et al., 2014). Also, it has been observed that auditory stimulation may increase activity in theta and sigma frequency bands just after the cue presentation (Creery et al., 2015; Farthouat et al., 2016; Fuentemilla et al., 2013; Schreiner and Rasch, 2014a; Schreiner et al., 2018). As shown by Schreiner and colleagues (2018) and by studies comparing acoustic against sham stimulation (see next sections), the theta and sigma activity enhancement may be related to cue-evoked K-complexes, which drive a stronger physiological response compared to spontaneous K-complexes. Interestingly, a very recent paper suggests that theta oscillations (at 5 Hz) may play a key role in orchestrating the reactivation of information both during sleep and wakefulness (Schreiner et al., 2018)

An important caveat of the acoustic TMR concerns the presentation of several consecutive tones during sleep. Indeed, two independent studies showed that the presentation of two cues separated by less than 1500 ms can impair memory consolidation (Farthouat et al., 2016; Schreiner et al., 2015), potentially because of the suppression of post-

cue spindle activity. This latter issue may be one of the factors explaining the lack of TMR benefits reported by several studies. Other factors may be the number of cues presented during sleep, the phase of ongoing EEG activity the cues are delivered in, and even participants' age. For instance, a recent study showed that the typical benefit of auditory TMR on language learning is not observed in older adults, who also show a lack of physiological responses (e.g., increased theta and spindles activity) to the auditory cues during sleep (Cordi et al., 2018)

Overall, these studies showed that TMR is a potential tool exploiting sensory stimulation during sleep to shape memory consolidation by modifying the underlying memory-related sleep physiology. However, not all sensory cues produce equivalent outcomes. For example, odors are highly reliable in enhancing declarative memory consolidation, but they produce no benefit for procedural memories (for reviews see (Cellini and Capuozzo, 2018; Schouten et al., 2017)). Acoustic stimulation is less reliable (i.e., some studies reported no beneficial effect, see (Cellini and Capuozzo, 2018; Schouten et al., 2017)), but can be successfully used to enhance motor skills (Schönauer et al., 2014). Moreover, acoustic stimulation can be performed with non-invasive equipment (e.g., earphones or speaker) and can be used in combination to wearable systems. Cue volume amplitude is an important consideration, in that louder cues may disturb sleep and softer cues may not infiltrate the sleeping brain. Also, using a single volume amplitude across subjects (in these studies ranging from 35 to 55 dB SPL using loudspeakers) may be problematic due to individual differences in auditory thresholds. Of note, while most of the studies have selected the volume levels based on sound pressure level (i.e., the output of the earplugs or of the loudspeakers), some studies have used hearing level intensity (i.e., what an individual is able to hear) (Sterpenich et al., 2014).

Another important caveat of this approach is that it requires pretraining of the association between the sensory cue and the target during wakefulness. Moreover, since several consecutive stimuli can impair the memory process, rather than improve it, the delivery of the stimulation must be carefully timed. Lastly, it seems that several reiterations of the sensory cues are needed to promote a meaningful benefit in memory performance (e.g., increased memory accuracy, reduced forgetting). While TMR remains a useful and reliable method to modulate memory processing during sleep, these caveats seem to limit the feasibility of a daily, out of the lab, employment of this approach.

2.2. Stimulating with non-meaningful sounds: Rhythmic and closed-loop auditory stimulation

Building on the limitations of the TMR approach and on the advancement of knowledge of the physiology underlying memory processes during sleep, other methods have been developed using stimulation during sleep with non-meaningful cues, such as rhythmic and closed-loop auditory stimulation.

As mentioned in the introduction, it has been known for almost 80 years that the presentation of acoustic tones during sleep is able to elicit a SO/K-complex followed by slow or fast spindles, whereas entraining the ongoing EEG activity using 6 Hz sounds has little success (Davis et al., 1939). More recently, several studies showed that acoustic stimulation during sleep not only can evoke K-complexes (Colrain, 2005) but in general increases SO and slow wave activity (SWA; 0.5–4 Hz)(for a review see (Bellesi et al., 2014)).

A couple of studies have recently attempted to use rhythmic sequences of acoustic stimuli to enhance specific sleep oscillations. Ngo and colleagues tested the effect of either 0.8 Hz or random auditory stimulation (60 dB SPL, using in-ear headphones) with an inter-stimulus interval (ISI) between 1.25 s to 5 s (Ngo et al., 2013a). They observed that the 0.8 Hz stimulation increased SO power after 10–15 minutes from the beginning of the stimulation compared to the random stimulation and a sham condition. Moreover, the 0.8HZ stimulation induced more trains of SOs during SWS compared to the other conditions.

In a recent paper, Simor et al., (2018) tested the effect of rhythmic stimulation delivered unilaterally (only through one ear) during NREM sleep. The stimulation consisted of 12 bursts of pink noise delivered at 1 Hz (12 s-on/15-s off), with volume initially set to the individual's auditory threshold and then increased throughout the stimulation up to 60 dB. Compared to non-stimulated epochs, rhythmic stimulation induced evoked k-complexes bilaterally, increased EEG activity in the slower delta range (0.75–2.25), and entrained theta and sigma activity immediately after the first pulse.

Another study used oscillating auditory cues (white noise presented at 42 dB SPL) with a frequency of 12 Hz and 15 Hz (resembling slow and fast spindles, respectively) delivered during NREM in a 2 s-on 8s-off sequence (Antony et al., 2018a). The authors observed that the stimulation was able to modulate parietal sleep spindles in a frequency-specific fashion, i.e. slow spindles increased in response to 12 Hz whereas fast spindles were enhanced by the 15 Hz sequence. In another study, the authors delivered acoustic stimuli either at 14 Hz or 40 Hz in a 1 s-on/3 s-off fashion throughout a daytime nap (Lustenberger et al., 2017). However, this time the authors did not see any frequency-specific modulation of the stimulation. Instead, both sounds were able to elicit an increase in spindle activity compared to the sham.

Similarly to TMR, timing matters for rhythmic auditory stimulation. Indeed, when open-loop auditory stimulation (i.e., three clicks separate by 1.075 s) was applied during NREM sleep (Weigenand et al., 2016), the authors observed an increase in SO power, but also a reduction in phase-locked spindle activity and no memory improvement compared to a control sleep condition. Taken together, these results indicate that, for acoustic stimulation, the timing of the stimulation is a critical factor to allow the reactivation process to unfold.

These scientific advancements have led to the development of technological innovations in which the delivery of sensory stimuli is triggered by specific sleep events, avoiding the timing problems observed by the TMR and the rhythmic stimulation. In a seminal paper, Ngo et al., (2013b) developed an auditory closed-loop feedback system able to detect online SO activity and then deliver a brief auditory stimulation (i.e., 50-ms bursts of pink noise at 55 dB SPL) during the SO up-state (Fig. 2). This system was based on an adaptive amplitude threshold method (with default value set at -50μV), and it was able to increase SO power, to boost spindle activity phase-locked to the SO up-state and, remarkably, to increase memory performance in a word-pair association task relative to a control condition. These findings were further replicated in another study by the same group (Ngo et al., 2015). These papers opened the field to the idea that sensory stimulation may be performed by targeting specific oscillatory events, allowing a more precise control of the stimulation and the related outcomes. Following these papers, other research groups have developed similar systems. Santostasi et al., (2015) created a system based on a phase-locked procedure to predict the phase of a SO (of at least -50μV of amplitude) and to deliver a 50-ms pink noise stimulus in the transition from the down to the up state of the SO. Of note, the sound had a volume ranging between 30 to 48 dB, based on individualized auditory thresholds determined automatically by the system. With this system, they were able to consistently target the SO at the 240° (with down phase at 90° and up phase at 270°). When they applied this system to young (Ong et al., 2016) and older (Papalambros et al., 2017) adults to test the effect at the physiological and behavioural level, using trains of 5 consecutive sounds separated by 1.2 s intervals, they observed an increase in SWA, which was associated with enhancements in declarative memory consolidation compared to a sham stimulation. Another study using the same system in young adults, but applying a single 50-ms pink noise instead of a train of pulses, also showed an enhancement in SWA, spindle activity and memory performance in a word-pair association task (Leminen et al., 2017). However, the same study showed no performance improvement after stimulation on a serial finger tapping task, picture recognition, and face-name association. The authors suggested that their null result may have resulted from the difficulty of the task, the "mixture" of verbal and semantic stimuli (for

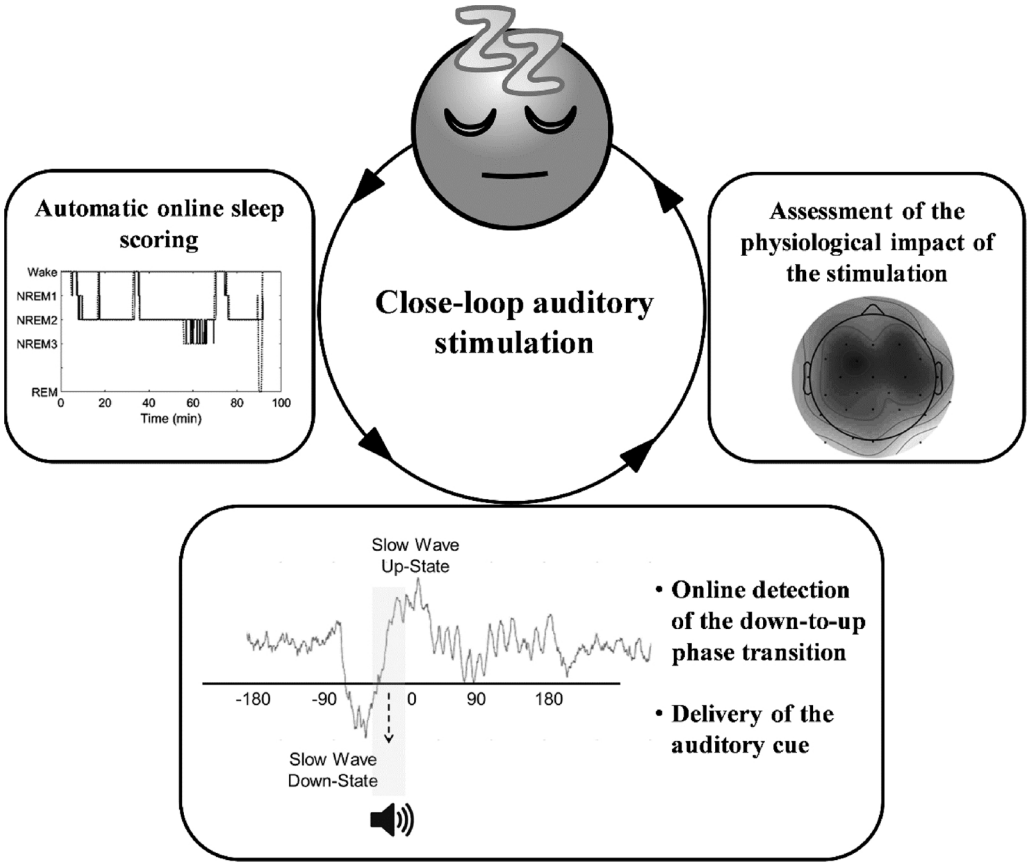

Fig. 2. Cartoon of an auditory closed-loop stimulation paradigm. The participant' sleep is automated scored online. When the participant reaches a specific sleep stage (e.g., N2 or SWS), the down-to-up phase transition of a slow oscillation is detected, and an auditory cue is delivered. The effect of the acoustic stimulation is then assessed at the physiological level (e.g., increase slow oscillation amplitude and duration).

the face-name associations), the use of a recognition rather than a recall paradigm (for the picture task). For the procedural task, they suggested that improvement on this task relies on N2 and REM sleep rather than N3 sleep. It is also highly possible that the sleeping brain could not bear the encoding and the consolidation of 4 tasks in the same night, therefore prioritizing pure verbal information at the expense of the other material.

Another group has recently investigated the effect of daytime nap acoustic stimulation of SO on the post-sleep encoding of visual memories (i.e., pictures) (Ong et al., 2018). They developed a system able to perform a real-time sleep scoring using a deep learning approach (Patanaik et al., 2018) and to detect the up phase of the SO based on an adaptive voltage threshold (starting from -75 μV). When SOs were detected, the system delivered a 40 ms pink noise with an intensity of 16 dB above the wake hearing threshold in a 2-on/2-off fashion. Using a within-subjects design with a large sample (N = 36) they showed that the stimulation during the nap enhanced low frequency (delta and theta) and spindle-frequency (9–15 Hz) power and the duration of SWS, compared to sham. In addition, although memory performance did not differ between stimulation and sham, the individuals who showed the greater SO-evoked response to the stimulation had the higher memory performance, and the SO-evoked response was associated with larger anterior hippocampal activation at encoding (assessed via fMRI). This study confirmed that acoustic stimulation during sleep modulates the SO and subsequent spindle response, but it failed to show any memory improvement compared to sham. Considering that participants were partially sleep deprived before the daytime nap (the night before the experiment, their sleep time was restricted to the 1:00-5:00 a.m. window to increase sleep propensity the next day), it is possible that in both conditions (sham and stimulation) participants experienced, during the post-sleep deprivation nap, a strong increase in SWS due to an homeostatic rebound, which was enough to perform the post-nap task up to their individual limit.

A different group (Debellemaniere et al., 2018) has recently tested in a very large sample (about 1000 nights) an ambulatory EEG device with dry electrodes which delivers a 40 dB 50-ms **pink** noise on the down-to-up phase of a SO (approximately at 45°, with down phase at 270° and up phase at 90°). Their system uses a machine learning algorithm to identify N3 in real time and a phase fitting algorithm (see Cox et al., 2014) to detect the SOs. With this system, they showed an increased SWA in the 4 s after the stimulation. More interestingly, this study showed that the same effect on SWA was observed after 10 days of stimulation, suggesting that the sleeping brain does not adapt to the stimulation at least over a 10-day period, indicating that night-by-night acoustic stimulation may be a feasible approach to continuously modulate SO activity over time. Unfortunately, the authors did not report any information about the effect of the stimulation on spindle activity and cognitive performance.

Recently, Ngo et al., (2018) aimed to deliver a cue that resembled the frequency of each individuals' fast spindle (on average 13.4 Hz) during the down-to-up phase transition (about 190 ms after the down peak of the SO). This auditory cue was composed of seven clicks of 25-ms pink noise spaced by a constant time interval (e.g., 50 ms). Comparing this stimulation against an "arrhythmic" (seven clicks spaced by a jitter duration between 5–138 ms) and a sham stimulation, they observed that both stimulations induced a delayed increased activity in fast spindles during the SO up phase (i.e., 500–1500 ms post-cue). Moreover, the spindle-like stimulation did not increase the total number of spindles and did not facilitate memory retention in a word-pair association task, compared to sham. The authors suggested that the spindle-like stimulation, instead of being able to entrain the spindle activity, impaired the endogenous expression of SO-spindle events. Of note, some studies report that, compared to sham, acoustic stimulation enhances both theta and sigma activity (Papalambros et al., 2017; Ong et al., 2016, 2018). For example, Papalambros and colleagues (2017), comparing the EEG activity after stimulated and non-stimulated SOs,

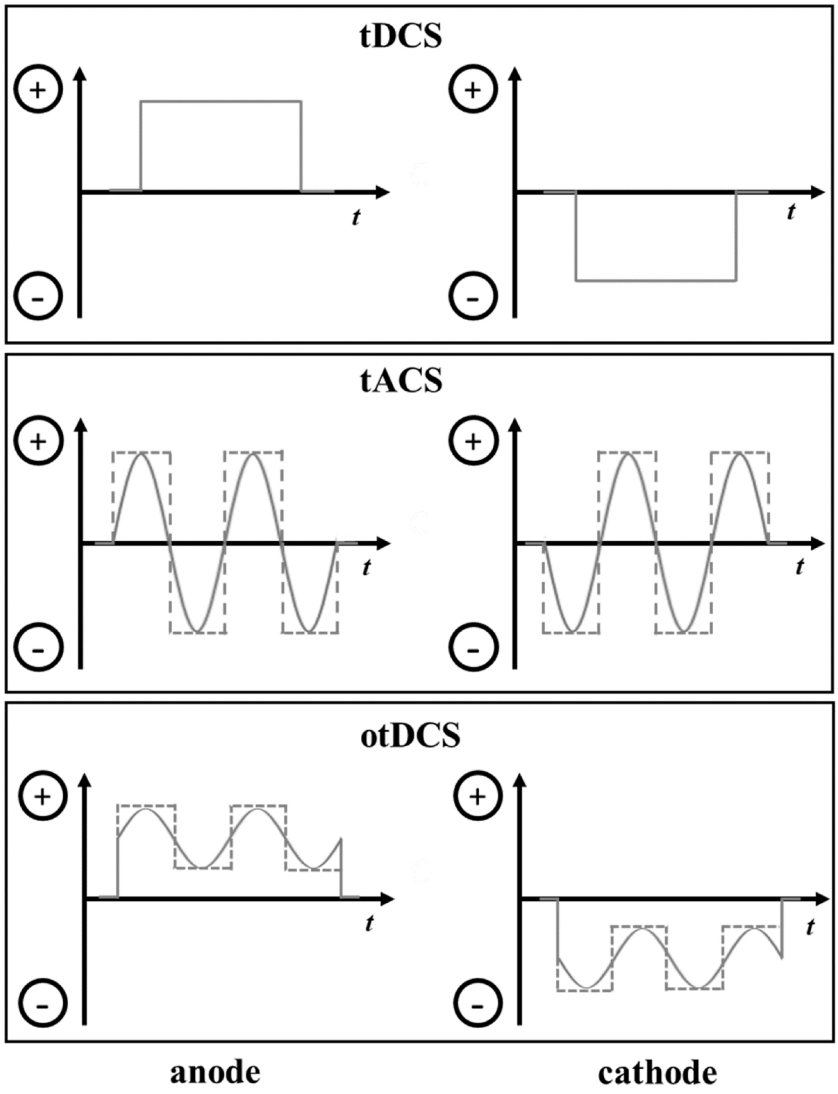

Fig. 3. Schematic representation of transcranial electric stimulations (tES). Upper panel: In the transcranial direct current stimulation (tDCS), the current is constantly delivered for a period of time (typically few minutes) either from the negative to positive polarity site (anodal stimulation) or in the other direction (cathodal stimulation). **Middle panel:** In the transcranial alternate current stimulation (tACS), the current is alternating at a specific frequency flowing from the cathode to the anode (anodal tACS) or in the other direction (cathodal tACS) and then flipping back and forth between electrodes. The current can be either sinusoidal (solid line) or squared (dotted line). **Lower panel:** The oscillatory tDCS (otDCS) is a combination of tDCS and tACS, in which the oscillatory current is coupled with a direct current, either positive (anodal otDCS) or negative (cathodal otDCS). Similar to tACS, the current can be sinusoidal or squared. Note that the slow oscillatory tDCS described in the review is an otDCS with a positive DC offset and a current oscillating at 0.75 Hz. Also note that another tES, namely random noise stimulation, is not reported here due to lack of studies using this technique with sleep. The figure is adapted from (Herrmann et al., 2013).

showed increased theta activity 500 ms after the cue, and increased sigma activity after 1000 ms and 3000ms

2.3. Combining TMR with closed-loop stimulation

The studies using closed-loop acoustic stimulation induced performance enhancements in declarative tasks by increasing slow wave and phase-locked sigma activity. However, this approach lacks the specificity of TMR to enhance individual memory items. Recently, Shimizu and colleagues (2018) developed a system that combines closed-loop stimulation with TMR (CL-TMR). Specifically, the CL-TMR detects the ongoing EEG activity by computing the ratio of spectral power in delta, alpha, and gamma in different electrode sites (to score sleep online) and identifies SOs as oscillations that cross a -80μV amplitude threshold (based on the average activity of frontal channels). Then, the system delivers specific auditory cues (whose volume varies according to individual auditory threshold), which were previously associated with learning materials, during the up-state of the SO (about 200 ms after the negative peak of SO). Applying this technique following encoding in a virtual reality spatial navigation task facilitated navigation efficiency, compared to a no stimulation condition. In addition, replicating previous findings, stimulation enhanced spindle activity locked to the up-state of the SO. A modest increase in theta activity just after cue presentation was also found. However, it should be noted that the authors could not disentangle whether the observed behavioural and physiological effects were due to the auditory cue per se or to the timed stimulation during the SO up-state.

More recently, Antony and colleagues (2018a) showed that when a spindle followed an auditory cue, participants increased their post-sleep performance in a spatial memory task, whereas when a spindle occurred just before the cue, memory retention was impaired. Based on these results, they hypothesized that spindle activity has a refractory period of about 3 s, and if an auditory cue is presented in this period, the sleeping brain is not able to process it. To directly test this idea, they developed a closed-loop system to deliver TMR cues (~40 dB) just after (0.5 s after a spindle was detected) or later (2.5 s after a spindle). The results confirmed their hypothesis: auditory cues presented outside the refractory period led to greater memory performance relative to the condition in which the cue was presented just after the spindle. This study not only extended previous studies showing that a “silent” period is needed between sensory stimuli in order to facilitate memory processing (Farthouat et al., 2016; Schreiner et al., 2015), possibly protecting memory reprocessing from interference (Antony et al., 2018b), but also showed that targeting sleep spindles may be a feasible approach to optimize sleep-related memory processing.

Overall, these studies provide compelling evidence that the temporal coupling between SO and fast spindles may be the critical physiological mechanism underlying memory consolidation during sleep, and that this mechanism can be manipulated by delivering an auditory cue during the transition from the down to the up-phase of the SO.

Moreover, the timing of the stimulation is critical in order to let the memory processing unfold. Interestingly, stimulation during sleep does not appear to disrupt sleep architecture, suggesting that these interventions do not impair sleep quality. Remarkably, different sleep features may be targeted (e.g., SO, spindles) depending on the study goals, and the TMR approach can be combined with a closed-loop delivery system (Antony et al., 2018a; Shimizu et al., 2018). Nevertheless, we are still in need of studies assessing the long-term effects (at the psychological and behavioural level) of stimulations repeated over several nights (but see (Debellemaniere et al., 2018)), and further investigations are required to clearly quantify the safety of these protocols over time.

3. Non-invasive brain stimulation (NIBS)

Non-invasive brain stimulation (NIBS) refers to a set of techniques which use electrical (i.e., transcranial electrical stimulation, tES) or magnetically-induced (i.e., transcranial magnetic stimulation, TMS) currents in order to excite or inhibit brain activity in a specific brain region (Liew et al., 2014). In particular, tES has been applied during sleep in several studies aimed to enhance memory performance compared to a sham (no stimulation) condition. The tES protocols are purported to induce a synchronization of the ongoing brain activity with the frequency (and, in some cases, the shape) of the electrical current delivered.

In 2004, Marshall and colleagues applied a specific tES, namely anodal transcranial direct current stimulation (tDCS, Fig. 3), with current constantly delivered at 0.75 Hz (with current density of 0.26 mA cm^{-2} applied in a 15 s-on/15 s-off fashion), during SWS (using F3 and F4 as positive polarity sites and the mastoids as the reference), showing that the stimulation increased declarative memory performance (i.e., word pairs task). At the physiological level, the stimulation enhanced EEG activity below 3 Hz, reduced the EEG power in the 4–10 Hz range and the number of spindles, compared to a sham condition. This result was further replicated by the same group in a seminal paper using an anodal slow oscillatory tDCS (so-tDCS, Fig. 3) with a sine wave of 0.75 Hz, during NREM sleep (Marshall et al., 2006). In this latter study, the effect of the stimulation was pronounced for frontal SOs (.5–1 Hz) and slow sigma frequency (8–12 Hz). Discrepancies between these studies may be due to differences in the type of stimulation used. While in the first study Marshall and colleagues use a "standard" anodal tDCS (i.e., the current is constant over time and flows from the negative to the positive site), in the 2006 study they used an anodal so-tDCS (i.e., a combination of DC and AC stimulation, with the current cyclically increasing and decreasing in its intensity) applied for 5 min on/1 min off. Of note, to match the current intensity of the first study, in 2006 Marshall et al. increased the current density to 0.517 mA cm^{-2}. Despite the technical differences, both papers show electrical modulation of SOs resulting in post-sleep memory benefit. However, the exact mechanism underlying this modulation is not still not well understood. It is possible that the anodal stimulation, which is supposed to enhance the activity of the stimulated area may have modulated SO activity by increasing the probability of action potentials occurring in prefrontal regions, where SOs are generated (Murphy et al., 2009).

Another possibility is that the use of an oscillatory stimulation with a montage that includes mastoids may have induced a galvanic vestibular stimulation, which in turn may have increased slow activity (see Bayer et al., 2011 and the Vestibular and Tactile Stimulation section below). Also, a potential impact of cutaneous co-stimulation typical of the tDCS cannot be excluded (see Thair et al., 2017).

Subsequent studies using similar protocols (i.e., 0.75 Hz oscillating stimulation) in healthy young and older adults, as well as in children with attention-deficit/hyperactivity disorders, patients with mild cognitive impairment, temporal lobe epilepsy or schizophrenia, showed the same beneficial effect at the behavioral level (Göder et al., 2013; Antonenko et al., 2013; Del Felice et al., 2015; Ladenbauer et al., 2017; Prehn-Kristensen et al., 2014; Westerberg et al., 2015), sometimes also showing an enhancement in fast spindles activity (Ladenbauer et al., 2016; Paßmann et al., 2016; Marshall et al., 2006). However, some studies failed to show a beneficial effect of tDCS or other tES techniques like transcranial alternative current stimulation (tACS, Fig. 3) on memory consolidation (Eggert et al., 2013; Paßmann et al., 2016; Sahlem et al., 2015). Eggert and colleagues (2013) showed no benefit of SO-tDCS on either a word-pair association task or a finger tapping task in 26 healthy elderly participants (60–90 years old). In addition, they showed that -tDCS, compared to sham, disturbed participants' sleep architecture (i.e., increased time awake and less SWS). As noted by the authors, possible explanations for these results may be the age of the participants, as well as some changes in the stimulation protocol relative to previous studies (e.g., a current density of 0.331 mA cm^{-2}, almost half of that used by Marshall et al., 2006). However, similar results were reported by Paßmann and colleagues (2016), who tested 21 older adults (50–80 years old) on a visuo-spatial, a verbal, and a finger tapping task. They showed no beneficial effect of the stimulation on memory performance in the verbal and procedural tasks and an impairment in the visuo-spatial task. At the physiological level, power increased in frontal SO and slow sigma compared to sham, but also an increased time spent awake and a reduction in time spent in sleep stage 4. Sahlem and colleagues (2015) tried to replicate the Marshall et al. (2006) findings using the same protocol but with a square wave instead of a sinusoidal oscillation (see also Fig. 3). They failed to replicate the original findings at the behavioral level (no memory benefit), although they showed a trend to a similar physiological modulation (increase in frontal SWA and slow spindles activity). It remains unclear whether this contrasting finding was due to the different wave used, hardware differences, or subject population.

Nevertheless, a meta-analysis of the studies published up to 2016 supported the idea that tES can enhance declarative memory consolidation when applied during NREM (but not when delivered during REM, see (Marshall et al., 2011)). However, this approach does not facilitate procedural memory consolidation (Barham et al., 2016). As recently suggested by Koo et al., (2018), these heterogeneous findings may be due to differences in stimulation parameters, tasks, and inter-individual factors, such as individual memory skills. Interestingly, the same technique has been used to successfully disrupt memory consolidation processes (e.g., using cathodal stimulation at 5 Hz during SWS, (Garside et al., 2015; Marshall et al., 2011)). Of note, with the exception of Nitsche et al., (2010), who used active electrodes placed near C3 with reference electrodes above the right eye, all the other studies placed the active electrodes in frontal sites (F3 and F4 or in one case F7 and F8, (Westerberg et al., 2015)) and the references over the mastoids.

A different and very interesting approach has been used by Lustenberger et al., (2016). They developed a feedback-controlled tACS system able to detect online sleep spindles during NREM and then to deliver a brief (about 1 s) spindle-like waveform (12 Hz) alternating current in frontal regions (i.e., F3 and F4) locked to the spindles. Compared to a sham, they observed a general increase in spindle activity (11–16 Hz) during N2 but also reduced delta and theta activity across the whole scalp. At the behavioral level, this stimulation enhanced motor memory consolidation (i.e., in a finger tapping task) compared to sham. Moreover, the increase in fast spindles activity (15–16 Hz) was associated with higher memory performance (i.e., increased tapping speed). This paper introduced two important breakthroughs in the field: 1) the use of a closed-loop tES to target sleep spindles, and 2) the use of a spindle-like waveform instead of a "frequency" stimulation (e.g., slow oscillation, theta frequency).

In conclusion, several open questions remain. Among them, what is the impact of tES on sleep physiology? Are the observed beneficial effects on memory performance due to the increased SO activity per se or to the concurrent temporal coupling between SO and spindles? To date, these questions remain unanswered because of an important limitation

of tES, i.e., the electrical stimulation produces EEG artifacts that can last for several seconds. Therefore, a precise evaluation of the acute consequence of stimulation, including the temporal relationship between SOs and sigma/spindles, cannot be assessed. In terms of therapeutic application, many questions also remain. How long is tES stimulation beneficial (e.g. habituation effects)? What are the long-term physiological consequences of daily stimulation? Similar to many novel intervention approaches, long-term behavioral and physiological data is lacking, and further research is required to fill this gap.

4. Vestibular and tactile stimulation

Stimulation of the vestibular system, which processes information about motion, balance and spatial orientation, can be done by swinging and rocking or by inducing the sensation of rocking via electrical stimulation to the vestibular nerves. Electrical stimulation of the vestibular nerves seems to shorten sleep onset latency (Krystal et al., 2010), whereas sleeping on a bed rocking at 0.25H also induced a shortened sleep onset coupled with an increased amount of N2 sleep and of SWA power (here measured in the 0.6–5 Hz range)(Bayer et al., 2011). Based on these results, Omlin et al., (2018) recently tested the effect of vestibular stimulation on sleep physiology and declarative memory consolidation (word-pair learning task) using a “rocking bed” (at either 0.16 Hz or 0.24 Hz). Although the authors reported an increase in the number of spindles in the first 2 h of sleep (but not across the whole night), no change in SO activity or in memory performance compared to a baseline night (no stimulation) was observed.

Although it cannot be concluded from this study that stimulation is effective in modulating memory-related sleep physiology, the use of a “rocking bed” stimulation is indeed intriguing. Potentially, since it does not require a complicated set-up such as electrodes montage or a brain-computer interface system, this stimulation can be easily used outside the lab by the general population. Moreover, it can be used with in-patients and, potentially, with individuals recovering from brain damage (e.g., stroke) or suffering dementia (Alzheimer disease). However, further studies are needed to understand whether and how this stimulation may be beneficial for memory-related sleep physiology.

The effect of tactile stimulation during sleep has received little attention. Tononi et al., (2010) reported only minor effects on SWA after median nerve stimulation. Pereira et al., (2017) used a light stimulation on the participants’ fingers during NREM sleep in a TMR protocol testing motor skill learning. They showed an increase in SO density and a reduction of spindle activity after the stimulation, but no memory benefit was observed.

5. Pharmacological approach

Pharmacological approaches have been used as a method to test the significance of a single neurotransmitter (e.g., acetylcholine) or to test the impact of enhancing a specific sleep feature (e.g., zolpidem to enhance sigma activity) on memory consolidation. An important study by Gais and Born (2004) tested the Hasselmo model of a dynamic role of acetylcholine in memory formation (Hasselmo, 1999). Central nervous cholinergic transmission during SWS-rich sleep was increased in healthy participants by administering an infusion of 0.75 mg of the cholinesterase inhibitor physostigmine, after the encoding of word pairs, which completely blocked SWS-related consolidation of declarative memories. This finding was important for two reasons: 1) it provided the first support for acetylcholine’s critical role in sleep-dependent memory consolidation in humans, and 2) it provided a novel method for testing causal relationships between sleep and memory using pharmacological interventions in humans. Following this, Rasch et al., (2009) demonstrated that selective REM sleep suppression (obtained through administration of selective serotonin or norepinephrine re-uptake inhibitors) after training did not impair consolidation of skills or word-pairs in healthy men but rather enhanced gains in finger tapping accuracy, likely by increasing sleep spindle activity. Interestingly, a recent study by the same research group combined a pharmacological approach with olfactory TMR (Klinzing et al., 2017). Specifically, the authors increased again the cholinergic tone of the participants using physostigmine, which effectively augmented the accumulation of acetylcholine at the synaptic level. During SWS, they presented olfactory cues previously associated with a target item to be remembered. The authors expected that physostigmine would block hippocampal-neocortical communication resulting in a reduced post-sleep memory performance. Contrary to this hypothesis, the participants benefitted from the odor stimulation even in a high cholinergic state. This finding challenged the idea that TMR modulates the hippocampal-neocortical communication and suggested, instead, that TMR may strengthen memories at the hippocampal level, in line with results from Diekelmann et al. (2011).

Feld and colleagues conducted a series of double-blind, placebo-controlled, within-subjects, crossover design studies testing the effect of different drugs on modulating memory-related sleep physiology. In one study (Feld et al., 2013b) they stimulated GABAergic neurotransmission using tiagabine (10 mg), a GABA reuptake inhibitor, in order to increase SWS at the expense of REM sleep. They tested the effect of this stimulation on overnight consolidation of declarative, emotional and procedural memories in young adults, showing two opposite results. On the one hand, the tiagabine increased the time spent in SWS, the density of SOs, and the power of slower EEG bands (.5–8 Hz). On the other hand, performance in the declarative and emotional task did not differ between placebo and tiagabine conditions, showing also a post-stimulation impairment in the procedural task performance. As explained by the authors, this rather surprising effect was likely due to decreased spindle density during N2 sleep and to the reduced synchronization between SOs and spindles in the tiagabine compared to the placebo condition.

In another study with a similar design, the same group conducted three experiments to test the role of glutamatergic neurotransmission in sleep-related memory processing (Feld et al., 2013a). In the first two experiments, they used an NMDA receptor blocker (ketamine: 0.25 mg/kg) and an AMPA receptor blocker (caroverine, 40 mg) to inhibit glutamatergic transmission and impairing overnight memory consolidation. In a previous study caroverine (80 mg) and ketamine (0.25 mg/kg) were shown to impair post-sleep performance on a visual texture discrimination task, indicating a key role of glutamatergic neurotransmission in the consolidation of visual information (Gais et al., 2008). In the third experiment, the authors used an NMDA receptor co-agonist (D-cycloserine (DCS), 175 mg), to facilitate memory retention.. They showed that the NMDA and the AMPA blockers did not impair memory consolidation, whereas the DCS facilitated the consolidation of declarative (but not procedural) information while increasing N1 and reducing REM sleep). The authors proposed that glutamatergic neurotransmission during sleep may be involved in both synaptic potentiation (i.e., consolidation) and downscaling (i.e., forgetting). In a recent pre-print, the same groups showed that DCS also facilitated the post-sleep encoding of new declarative information (Asfestani et al., 2018).

The same group also tested the effect of pramipexole (0.5 mg), a D2 dopamine receptor agonist, on overnight retention of pictures associated with low and high monetary reward, as well as in a standard declarative and procedural task (Feld et al., 2014). Although the overall performance was not affected by the drug, purportedly due to the induced suppression of SWS and REM sleep, pramipexole affected the quality of performance: with decreased benefit of the high reward, compared with placebo. Furthermore, Feld et al., (2016), tested the effect of intranasal insulin, previously associated with enhanced memory encoding (Benedict et al., 2004, 2007), on overnight declarative and procedural consolidation, using an interference paradigm. The authors showed that intranasal insulin (1.6 ml insulin) affects sleep neurophysiology (i.e., increased growth hormone concentration and EEG delta activity) but it does not modulate memory consolidation.

However, this stimulation impaired the encoding of new material the following evening, suggesting that intranasal insulin may impair the renormalization of synaptic weights (Tononi and Cirelli, 2014), limiting the ability to learn new information.

In a series of studies that investigated the role of sleep spindles for hippocampal-dependent memory consolidation, our group compared zolpidem, a $GABA_A$ receptor agonist shown to enhance sigma activity, and sodium oxybate, which interacts with the $GABA_B$ receptor and has conversely been shown to decrease sigma activity. Initially, we conducted a dose-response study of zolpidem (5 mg and 10 mg) and sodium oxybate (2.5 g and 3 g) to determine the optimal dose of zolpidem for increasing the density of N2 sleep spindles (Brunner et al., 1991; Feinberg et al., 2000), and sodium oxybate for decreasing the density of N2 sleep spindles in an early morning nap (Mednick et al., 2013). The nap occurred at 8:30 AM to capitalize on circadian fluctuations in REM sleep (highest in the morning) and maximize differences in sleep stages between the drug and placebo conditions. Next, we conducted a double-blind, placebo-controlled study comparing the effect of three pharmacological interventions (10 mg zolpidem, 2.5 g sodium oxybate, and placebo) on the consolidation of information from three memory domains: verbal, motor, and perceptual. In line with prior studies, zolpidem increased sleep spindle density and decreased REM sleep. At the behavioral level, zolpidem improved verbal memory but decreased perceptual learning. However, no changes were found for motor learning across drug conditions. Verbal memory performance was significantly correlated with spindle density in zolpidem and placebo, and marginally in sodium oxybate. Interestingly, when spindle density was included as a covariate in verbal memory analysis as a function of the drug, the main effect of drug condition disappeared, while the spindle density effect on performance was highly significant. In a second study, we compared the effect of zolpidem, sodium oxybate and placebo on memory for pictures that varied across two dimensions: valence (positive, neutral and negative) and arousal (high and low). We found that zolpidem increased memory for the negative and high arousal pictures significantly more than placebo, suggesting that spindles may be involved with emotional memory more so than REM sleep, which was not related to task performance (Kaestner et al., 2013).

Taken together, these results indicated that the verbal memory improvements with zolpidem may represent an enhancement of a normal consolidation process during sleep since similar correlations between spindles and verbal memory were found in all three drug conditions. In addition, the experimental manipulation of spindles and the associated increase in verbal memory raises the possibility that sleep spindles may represent physiological processes critical for declarative verbal memory consolidation, evinced by the significant effect of spindles on performance in the covariate analysis

It should be noted that long-term negative side effects may be expected for most of the pharmacological interventions. For example, the dopamine agonists may increase the risk of sleep attack but they can also augment the risk of developing sleep apnea (at least in patients with Parkinson disease (Borovac, 2016)) and insomnia symptoms (Ruigt and van Gerven, 2018). Similarly, drugs targeting the cholinergic system, due to their stimulant action, may impair sleep architecture (Ruigt and van Gerven, 2018). For example, using a cholinesterase inhibitor (i.e., galantamine), Biard et al., (2015)showed that, compared to placebo, the administration of the drug increases the proportion of REM, and reduced the latency and increased the proportion of REM at the detriment of N3 sleep. It also induced a more fragmented sleep (higher WASO, proportion of N1 and number of awakenings). Other studies showed that ketamine increases SWA (at least in patients with major disorders), but this effect decreases over a few nights (Duncan and Zarate, 2013). GABAenenrgic drugs seem to induce few adverse effects, mildly impacting sleep architecture, since they tend to boost the activity of endogenous GABA (Ruigt and van Gerven, 2018). Indeed, studies testing the effect of zolpidem in patients with insomnia showed positive effects in reducing sleep onset and increasing N3 and sleep efficacy, without reporting any side effects (Rummer et al., 1993; Walsh et al., 2000) (Rummer et al., 1993; Walsh et al., 200). However, zolpidem also showed a consistent decrease in REM sleep, which had subsequent negative impact on perceptual learning (Mednick et al., 2013).

All in all, although pharmacological interventions are interesting tools to probe a causal relationship between sleep physiology and memory processing, their application in free-living condition to promote changes in sleep-related processes is an area that needs more investigation into the long-term impact of these drugs and their potential to show continued benefit.

6. A wearable future?

Although most of the studies presented in this review were run in a laboratory setting, these stimulation techniques may be potentially used in free-living conditions. An example is the study by Debellemaniere and colleagues (2018), who combined a wearable device for automated sleep monitoring (Cellini et al., 2015) with a closed-loop system to deliver auditory cues, showing that at-home stimulation may be feasible for several days and can produce positive outcomes (e.g., increased SWA). Acoustic stimulation during sleep, either in a closed-loop or rhythmic fashion, seems to be the more feasible approach for free-living stimulation. Moreover, the developments in wearable sleep trackers, which are able to detect peripheral signals such as heart rate and claims to score sleep stage based on a combination of biosignals (de Zambotti et al., 2018), may give the opportunity to use cardiac signals as a proxy of the sleeping brain, providing a reliable temporal window for acoustic stimulation. Olfactory stimulation is more complex to conduct, but future studies may provide new insights into how to conduct these stimulations at home (for example using automated odor dispenser). The development of systems to perform odor stimulation in free-living conditions may be particularly important, considering that odors have been shown to modulate not only the consolidation of individual memories but also behaviors (Arzi et al., 2014; Cellini and Parma, 2015). Also, olfactory stimulation may be advantageous for populations such as individuals with autism spectrum disorder, who seems to be particularly sensitive to olfactory information (Parma et al., 2013) At home tES stimulations may be potentially feasible, given the portability of most of the equipment and the presence, on the market, of “over-the-counter” devices. However, tES may induce several moderate adverse events and, although there are no legal issues about using some of tES device at home without a clinical control, ethical aspects need to be carefully taken into account (Antal et al., 2017). Similarly, pharmacological interventions for treating sleep-dependent memory loss should be considered alongside all the potential caveats of any pharmacotherapy engenders.

Overall, it is possible to imagine a near future in which different types of simulations are performed during sleep using wearable devices. Although the speed that these devices will come to market may outpace researchers ability to evaluate their reliability and safety, similar to the path of wearable sleep trackers (de Zambotti et al., 2016). Therefore, researchers and companies alike need to consider not only legal but also ethical aspects of modulating the sleeping brain (Cellini and Parma, 2015). Lastly, it should be remarked that although some studies have tested the impact of brain stimulation techniques on more ecological (i.e., navigation task in a virtual reality environment, (Shimizu et al., 2018)) or more applied task (i.e., language learning, (Schreiner and Rasch, 2017)), most of the studies examine effect on controlled and simple laboratory tasks. Bringing these techniques in free-living conditions, to enhance or modulate real behaviors and cognitive processes, can indeed be a challenge, and their beneficial effects can be less effective than in a laboratory setting. Moreover, precautionary measures should be taken to avoid the use of wrong stimulation protocols, which can induce negative consequences to the ongoing brain activity, affecting several sleep functions. Lastly, current stimulation techniques

are far from able to be used in a therapeutic context. The few studies that have tried to use TMR with anxiety disorders failed to show any clinical benefits for the patients (Rihm et al., 2016; Groch et al., 2017) whereas there is a lack of data on the potential benefit of these techniques on sleep disorders (Cellini, 2017). All in all, real-world application as a goal requires that researchers test the effect of these techniques on more complex and ecological task.

7. Conclusion

Here, we provided a general summary of what interventions are currently used to stimulate the sleeping brain in order to modulate memory consolidation. Although the results are encouraging, suggesting that in general the sleeping brain may be optimized for better memory performance, the road to bring these techniques in free-living conditions is paved with unanswered questions and technical challenges that need to be carefully addressed.

Disclaimer

The authors declare no competing interests.

Acknowledgements

This work is supported by the University of Padova under the STARS Grants program to NC. SCM was supported by NIAR01AG046646. The present work was carried out in the scope of the research program “Dipartimenti di Eccellenza” from MIUR to the Department of General Psychology.

References

Antal, A., Alekseichuk, I., Bikson, M., et al., 2017. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin. Neurophysiol. 128, 1774–1809.
Antonenko, D., Diekelmann, S., Olsen, C., Born, J., Mölle, M., 2013. Napping to renew learning capacity: enhanced encoding after stimulation of sleep slow oscillations. Eur. J. Neurosci. 37, 1142–1151.
Antony, J.W., Gobel, E.W., O’hare, J.K., Reber, P.J., Paller, K.A., 2012. Cued memory reactivation during sleep influences skill learning. Nat. Neurosci. 15, 1114–1116.
Antony, J., Piloto, L.R., Wang, M., Pacheco, P., Norman, K.A., Paller, K.A., 2018a. Sleep spindle refractoriness segregates periods of memory reactivation. Curr. Biol. 28.
Antony, J.W., Schönauer, M., Staresina, B.P., Cairney, S.A., 2018b. Sleep spindles and memory reprocessing. Trends Neurosci.
Arzi, A., Shedlesky, L., Ben-Shaul, M., et al., 2012. Humans can learn new information during sleep. Nat. Neurosci. 15, 1460.
Arzi, A., Holtzman, Y., Samnon, P., Eshel, N., Harel, E., Sobel, N., 2014. Olfactory aversive conditioning during sleep reduces cigarette-smoking behavior. J. Neurosci. 34, 15382–15393.
Asfestani, M.A., Braganza, E., Schwidetzky, J., et al., 2018. Overnight memory consolidation facilitates rather than interferes with new learning of similar materials—a study probing NMDA receptors. Neuropsychopharmacology 43, 2292.
Barham, M.P., Enticott, P.G., Conduit, R., Lum, J.A., 2016. Transcranial electrical stimulation during sleep enhances declarative (but not procedural) memory consolidation: evidence from a meta-analysis. Neurosci. Biobehav. Rev. 63, 65–77.
Bayer, L., Constantinescu, I., Perrig, S., et al., 2011. Rocking synchronizes brain waves during a short nap. Curr. Biol. 21 R461-R62.
Bellesi, M., Riedner, B.A., Garcia-Molina, G.N., Cirelli, C., Tononi, G., 2014. Enhancement of sleep slow waves: underlying mechanisms and practical consequences. Front. Syst. Neurosci.(8).
Benedict, C., Hallschmid, M., Hatke, A., et al., 2004. Intranasal insulin improves memory in humans. Psychoneuroendocrinology 29, 1326–1334.
Benedict, C., Hallschmid, M., Schmitz, K., et al., 2007. Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology 32, 239.
Berkers, R.M., Ekman, M., Van Dongen, E.V., et al., 2017. Cued reactivation during slow-wave sleep induces connectivity changes related to memory stabilization. bioRxiv 185611.
Biard, K., Douglass, A., De Koninck, J., 2015. The effects of galantamine and buspirone on sleep structure: Implications for understanding sleep abnormalities in major depression. J. Psychopharmacol. (Oxford) 29, 1106.
Born, J., Wilhelm, I., 2012. System consolidation of memory during sleep. Psychol. Res. 76, 192–203.
Borovac, J.A., 2016. Focus: the Aging Brain: side effects of a dopamine agonist therapy for Parkinson’s disease: a mini-review of clinical pharmacology. Yale J. Biol. Med. 89, 37.
Brunner, D.P., Dijk, D.J., Munch, M., Borbely, A.A., 1991. Effect of zolpidem on sleep and sleep EEG spectra in healthy young men. Psychopharmacology (Berl.) 104, 1–5.
Buzsáki, G., 1989. Two-stage model of memory trace formation: a role for “noisy” brain states. Neuroscience 31, 551–570.
Cellini, N., 2017. Memory consolidation in sleep disorders. Sleep Med. Rev. 35, 101–112.
Cellini, N., Capuozzo, A., 2018. Shaping memory consolidation via targeted memory reactivation during sleep. Ann. N. Y. Acad. Sci. 1–20.
Cellini, N., Parma, V., 2015. Commentary: olfactory aversive conditioning during sleep reduces cigarette-smoking behavior. Front. Psychol. 6, 586.
Cellini, N., Mcdevitt, E.A., Ricker, A.A., Rowe, K.M., Mednick, S.C., 2015. Validation of an automated wireless system for sleep monitoring during daytime naps. Behav. Sleep Med. 13, 157–168.
Colrain, I.M., 2005. The K-complex: a 7-decade history. Sleep 28, 255–273.
Conte, F., Ficca, G., 2013. Caveats on psychological models of sleep and memory: a compass in an overgrown scenario. Sleep Med. Rev. 17, 105–121.
Cordi, M.J., Schreiner, T., Rasch, B., 2018. No effect of vocabulary reactivation in older adults. Neuropsychologia 119, 253–261.
Courtiol, E., Wilson, D.A., 2013. Thalamic olfaction: characterizing odor processing in the mediodorsal thalamus of the rat. J. Neurophysiol. 111, 1274–1285.
Cox, R., Hofman, W.F., De Boer, M., Talamini, L.M., 2014. Local sleep spindle modulations in relation to specific memory cues. Neuroimage 99, 103–110.
Creery, J.D., Oudiette, D., Antony, J.W., Paller, K.A., 2015. Targeted memory reactivation during sleep depends on prior learning. Sleep 38, 755–763.
Davis, H., Davis, P.A., Loomis, A.L., Harvey, E.N., Hobart, G., 1939. Electrical reactions of the human brain to auditory stimulation during sleep. J. Neurophysiol. 2, 500–514.
De Zambotti, M., Godino, J.G., Baker, F.C., Cheung, J., Patrick, K., Colrain, I.M., 2016. The boom in wearable technology: Cause for alarm or just what is needed to better understand sleep? Sleep 39, 1761–1762.
De Zambotti, M., Goldstone, A., Claudatos, S., Colrain, I.M., Baker, F.C., 2018. A validation study of Fitbit Charge 2™ compared with polysomnography in adults. Chronobiol. Int. 35, 465–476.
Debas, K., Carrier, J., Barakat, M., et al., 2014. Off-line consolidation of motor sequence learning results in greater integration within a cortico-striatal functional network. Neuroimage 99, 50–58.
Debellemaniere, E., Chambon, S., Pinaud, C., et al., 2018. Performance of an ambulatory Dry-EEG device for auditory closed-loop stimulation of sleep slow oscillations in the home environment. Front. Hum. Neurosci. 12, 88.
Del Felice, A., Magalini, A., Masiero, S., 2015. Slow-oscillatory transcranial direct current stimulation modulates memory in temporal lobe epilepsy by altering sleep spindle generators: a possible rehabilitation tool. Brain Stimulat. 8, 567–573.
Diekelmann, S., Born, J., 2010. The memory function of sleep. Nat. Rev. Neurosci. 11, 114–126.
Diekelmann, S., Büchel, C., Born, J., Rasch, B., 2011. Labile or stable: opposing consequences for memory when reactivated during waking and sleep. Nat. Neurosci. 14, 381–386.
Duncan, W.C., Zarate, C.A., 2013. Ketamine, sleep, and depression: current status and new questions. Curr. Psychiatry Rep. 15, 394.
Eggert, T., Dorn, H., Sauter, C., Nitsche, M.A., Bajbouj, M., Danker-Hopfe, H., 2013. No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimulat. 6, 938–945.
Farthouat, J., Gilson, M., Peigneux, P., 2016. New evidence for the necessity of a silent plastic period during sleep for a memory benefit of targeted memory reactivation. SSCUS 1, 14–26.
Feinberg, I., Maloney, T., Campbell, I.G., 2000. Effects of hypnotics on the sleep EEG of healthy young adults: new data and psychopharmacologic implications. J. Psychiatr. Res. 34, 423–438.
Feld, G.B., Lange, T., Gais, S., Born, J., 2013a. Sleep-dependent declarative memory consolidation—unaffected after blocking NMDA or AMPA receptors but enhanced by NMDA coagonist D-cycloserine. Neuropsychopharmacology 38, 2688.
Feld, G.B., Wilhelm, I., Ma, Y., et al., 2013b. Slow Wave Sleep Induced by GABA Agonist Tiagabine Fails to Benefit Memory Consolidation. Sleep 36, 1317–1326.
Feld, G.B., Besedovsky, L., Kaida, K., Münte, T.F., Born, J., 2014. Dopamine D2-like receptor activation wipes out preferential consolidation of high over low reward memories during human sleep. J. Cogn. Neurosci. 26, 2310–2320.
Feld, G.B., Wilhem, I., Benedict, C., et al., 2016. Central nervous insulin signaling in sleep-associated memory formation and neuroendocrine regulation. Neuropsychopharmacology 41 (1540).
Fogel, S., Vien, C., Karni, A., Benali, H., Carrier, J., Doyon, J., 2017. Sleep spindles: a physiological marker of age-related changes in gray matter in brain regions supporting motor skill memory consolidation. Neurobiol. Aging 49, 154–164.
Fuentemilla, L., Miró, J., Ripollés, P., et al., 2013. Hippocampus-dependent strengthening of targeted memories via reactivation during sleep in humans. Curr. Biol. 23, 1769–1775.
Gais, S., Born, J., 2004. Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. Proc. Natl. Acad. Sci. U. S. A. 101, 2140–2144.
Gais, S., Rasch, B., Wagner, U., Born, J., 2008. Visual–procedural memory consolidation during sleep blocked by glutamatergic receptor antagonists. J. Neurosci. 28, 5513–5518.
Garside, P., Arizpe, J., Lau, C.-I., Goh, C., Walsh, V., 2015. Cross-hemispheric alternating current stimulation during a nap disrupts slow wave activity and associated memory consolidation. Brain Stimulat. 8, 520–527.
Genzel, L., Kroes, M.C., Dresler, M., Battaglia, F.P., 2014. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? Trends Neurosci. 37, 10–19.
Genzel, L., Spoormaker, V., Konrad, B., Dresler, M., 2015. The role of rapid eye movement sleep for amygdala-related memory processing. Neurobiol. Learn. Mem. 122,

110–121.
Göder, R., Baier, P.C., Beith, B., et al., 2013. Effects of transcranial direct current stimulation during sleep on memory performance in patients with schizophrenia. Schizophr. Res. 144, 153–154.
Goel, N., Kim, H., Lao, R.P., 2005. An olfactory stimulus modifies nighttime sleep in young men and women. Chronobiol. Int. 22, 889–904.
Groch, S., Preiss, A., Mcmakin, D.L., et al., 2017. Targeted reactivation during sleep differentially affects negative memories in socially anxious and healthy children and adolescents. J. Neurosci. 37, 2425–2434.
Hasselmo, M.E., 1999. Neuromodulation: acetylcholine and memory consolidation. Trends Cogn. Sci. (Regul. Ed.) 3, 351–359.
Hauner, K.K., Howard, J.D., Zelano, C., Gottfried, J.A., 2013. Stimulus-specific enhancement of fear extinction during slow-wave sleep. Nat. Neurosci. 16, 1553–1555.
Herrmann, C.S., Rach, S., Neuling, T., Strüber, D., 2013. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front. Hum. Neurosci. 7, 279.
Hu, X., Antony, J.W., Creery, J.D., Vargas, I.M., Bodenhausen, G.V., Paller, K.A., 2015. Unlearning implicit social biases during sleep. Science 348, 1013–1015.
Huber, R., Ghilardi, M.F., Massimini, M., Tononi, G., 2004. Local sleep and learning. Nature 430 (78).
Jenkins, J.G., Dallenbach, K.M., 1924. Obliviscence during sleep and waking. Am. J. Psychol. 35, 605–612.
Kaestner, E.J., Wixted, J.T., Mednick, S.C., 2013. Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. J. Cogn. Neurosci. 25, 1597–1610.
Klinzing, J.G., Kugler, S., Soekadar, S.R., Rasch, B., Born, J., Diekelmann, S., 2017. Odor cueing during slow-wave sleep benefits memory independently of low cholinergic tone. Psychopharmacology (Berl.) 1–9.
Koo, P.C., Moelle, M., Marshall, L., 2018. Efficacy of slow oscillatory-transcranial direct current stimulation on EEG and memory–contribution of an inter-individual factor. Eur. J. Neurosci.
Krystal, A.D., Zammit, G.K., Wyatt, J.K., et al., 2010. The effect of vestibular stimulation in a four-hour sleep phase advance model of transient insomnia. J. Clin. Sleep Med. 6, 315.
Ladenbauer, J., Külzow, N., Passmann, S., et al., 2016. Brain stimulation during an afternoon nap boosts slow oscillatory activity and memory consolidation in older adults. Neuroimage 142, 311–323.
Ladenbauer, J., Ladenbauer, J., Külzow, N., et al., 2017. Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. J. Neurosci. 37, 7111–7124.
Leminen, M.M., Virkkala, J., Saure, E., et al., 2017. Enhanced Memory Consolidation Via Automatic Sound Stimulation During Non-REM Sleep. Sleep 40.
Li, W., Ma, L., Yang, G., Gan, W.-B., 2017. REM sleep selectively prunes and maintains new synapses in development and learning. Nat. Neurosci. 20, 427–437.
Liew, S.-L., Santarnecchi, E., Buch, E.R., Cohen, L.G., 2014. Non-invasive brain stimulation in neurorehabilitation: local and distant effects for motor recovery. Front. Hum. Neurosci. 8.
Lustenberger, C., Boyle, M.R., Alagapan, S., Mellin, J.M., Vaughn, B.V., Fröhlich, F., 2016. Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr. Biol. 26, 2127–2136.
Lustenberger, C., Patel, Y., Alagapan, S., et al., 2017. High-density EEG characterization of brain responses to auditory rhythmic stimuli during wakefulness and NREM sleep. Neuroimage.
Maingret, N., Girardeau, G., Todorova, R., Goutierre, M., Zugaro, M., 2016. Hippocampo-cortical coupling mediates memory consolidation during sleep. Nat. Neurosci. 19, 959–964.
Mak-Mccully, R.A., Rolland, M., Sargsyan, A., et al., 2017. Coordination of cortical and thalamic activity during non-REM sleep in humans. Nat. Commun. 8, 15499.
Maquet, P., Laureys, S., Peigneux, P., et al., 2000. Experience-dependent changes in cerebral activation during human REM sleep. Nat. Neurosci. 3, 831.
Marshall, L., Mölle, M., Hallschmid, M., Born, J., 2004. Transcranial direct current stimulation during sleep improves declarative memory. J. Neurosci. 24, 9985–9992.
Marshall, L., Helgadóttir, H., Mölle, M., Born, J., 2006. Boosting slow oscillations during sleep potentiates memory. Nature 444, 610–613.
Marshall, L., Kirov, R., Brade, J., Mölle, M., Born, J., 2011. Transcranial electrical currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS One 6, e16905.
Mednick, S.C., Cai, D.J., Shuman, T., Anagnostaras, S., Wixted, J.T., 2011. An opportunistic theory of cellular and systems consolidation. Trends Neurosci. 34, 504–514.
Mednick, S.C., Mcdevitt, E.A., Walsh, J.K., et al., 2013. The critical role of sleep spindles in hippocampal-dependent memory: a pharmacology study. J. Neurosci. 33, 4494–4504.
Mölle, M., Bergmann, T.O., Marshall, L., Born, J., 2011. Fast and slow spindles during the sleep slow oscillation: disparate coalescence and engagement in memory processing. Sleep 34, 1411–1421.
Murphy, M., Riedner, B.A., Huber, R., Massimini, M., Ferrarelli, F., Tononi, G., 2009. Source modeling sleep slow waves. Proc. Natl. Acad. Sci. 106, 1608–1613.
Ngo, H.-V.V., Claussen, J.C., Born, J., Mölle, M., 2013a. Induction of slow oscillations by rhythmic acoustic stimulation. J. Sleep Res. 22, 22–31.
Ngo, H.-V.V., Martinetz, T., Born, J., Mölle, M., 2013b. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 78, 545–553.
Ngo, H.-V.V., Miedema, A., Faude, I., Martinetz, T., Mölle, M., Born, J., 2015. Driving sleep slow oscillations by auditory closed-loop stimulation—a self-limiting process. J. Neurosci. 35, 6630–6638.
Ngo, H.-V.V., Seibold, M., Boche, D.C., Mölle, M., Born, J., 2018. Insights on auditory closed-loop stimulation targeting sleep spindles in slow oscillation up-states. J. Neurosci. Methods.
Nitsche, M.A., Jakoubkova, M., Thirugnanasambandam, N., et al., 2010. Contribution of the premotor cortex to consolidation of motor sequence learning in humans during sleep. J. Neurophysiol. 104, 2603–2614.
Norman, K.A., Newman, E.L., Perotte, A.J., 2005. Methods for reducing interference in the Complementary Learning Systems model: oscillating inhibition and autonomous memory rehearsal. Neural Netw. 18, 1212–1228.
O'reilly, R.C., Bhattacharyya, R., Howard, M.D., Ketz, N., 2014. Complementary learning systems. Cogn. Sci. 38, 1229–1248.
Omlin, X., Crivelli, F., Näf, M., et al., 2018. The effect of a slowly rocking bed on sleep. Sci. Rep. 8, 2156.
Ong, J.L., Lo, J.C., Chee, N.I., et al., 2016. Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation. Sleep Med. 20, 88–97.
Ong, J.L., Patanaik, A., Chee, N.I., Lee, X.K., Poh, J.-H., Chee, M.W., 2018. Auditory stimulation of sleep slow oscillations modulates subsequent memory encoding through altered hippocampal function. Sleep 41 zsy031.
Papalambros, N.A., Santostasi, G., Malkani, R.G., et al., 2017. Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. Front. Hum. Neurosci. 11.
Parma, V., Bulgheroni, M., Tirindelli, R., Castiello, U., 2013. Body odors promote automatic imitation in autism. Biol. Psychiatry 74, 220–226.
Paßmann, S., Külzow, N., Ladenbauer, J., et al., 2016. Boosting slow oscillatory activity using tDCS during early nocturnal slow wave sleep does not improve memory consolidation in healthy older adults. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation 9, 730–739.
Patanaik, A., Ong, J.L., Gooley, J.J., Ancoli-Israel, S., Chee, M.W., 2018. An end-to-end framework for real-time automatic sleep stage classification. Sleep 41 zsy041.
Pereira, S.I., Beijamini, F., Weber, F.D., Vincenzi, R.A., Da Silva, F.A., Louzada, F.M., 2017. Tactile stimulation during sleep alters slow oscillation and spindle densities but not motor skill. Physiol. Behav. 169, 59–68.
Perl, O., Arzi, A., Sela, L., et al., 2016. Odors enhance slow-wave activity in non-rapid eye movement sleep. J. Neurophysiol. 115, 2294–2302.
Poe, G., 2017. Sleep is for forgetting. J. Neurosci. 37, 464–473.
Prehn-Kristensen, A., Munz, M., Göder, R., et al., 2014. Transcranial oscillatory direct current stimulation during sleep improves declarative memory consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimulat. 7, 793–799.
Rasch, B., Born, J., 2013. About sleep's role in memory. Physiol. Rev. 93, 681–766.
Rasch, B., Büchel, C., Gais, S., Born, J., 2007. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315, 1426–1429.
Rasch, B., Pommer, J., Diekelmann, S., Born, J., 2009. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. Nat. Neurosci. 12, 396.
Rihm, J.S., Diekelmann, S., Born, J., Rasch, B., 2014. Reactivating memories during sleep by odors: odor specificity and associated changes in sleep oscillations. J. Cogn. Neurosci. 26, 1806–1818.
Rihm, J.S., Sollberger, S.B., Soravia, L.M., Rasch, B., 2016. Re-presentation of olfactory exposure therapy success cues during non-rapid eye movement sleep did not increase therapy outcome but increased sleep spindles. Front. Hum. Neurosci.(10).
Rudoy, J.D., Voss, J.L., Westerberg, C.E., Paller, K.A., 2009. Strengthening individual memories by reactivating them during sleep. Science 326 1079-79.
Ruigt, G.S., Van Gerven, J., 2018. The effects of medication on sleep and wakefulness. Sleep Disorders in Neurology: A Practical Approach 83–126.
Rummer, J., Guendel, L., Linden, J., et al., 1993. Long-term polysomnographic study of the efficacy and safety of zolpidem in elderly psychiatric in-patients with insomnia. J. Int. Med. Res. 21, 171–184.
Sahlem, G.L., Badran, B.W., Halford, J.J., et al., 2015. Oscillating square wave transcranial direct current stimulation (tDCS) delivered during slow wave sleep does not improve declarative memory more than sham: a randomized sham controlled crossover study. Brain Stimulat. 8, 528–534.
Santostasi, G., Malkani, R., Zee, P., Paller, K., 2015. A phase-locked loop for acoustic stimulation during slow-wave sleep. Sleep 38, A98.
Sara, S.J., 2017. Sleep to remember. J. Neurosci. 37, 457–463.
Schönauer, M., Geisler, T., Gais, S., 2014. Strengthening procedural memories by reactivation in sleep. J. Cogn. Neurosci. 26, 143–153.
Schouten, D.I., Pereira, S.I., Tops, M., Louzada, F.M., 2017. State of the art on targeted memory reactivation: sleep your way to enhanced cognition. Sleep Med. Rev. 32, 123–131.
Schreiner, T., Rasch, B., 2014a. Boosting vocabulary learning by verbal cueing during sleep. Cereb. Cortex 25, 4169–4179.
Schreiner, T., Rasch, B., 2014b. Boosting vocabulary learning by verbal cueing during sleep. Cereb. Cortex bhu139.
Schreiner, T., Rasch, B., 2017. The beneficial role of memory reactivation for language learning during sleep: a review. Brain Lang. 167, 94–105.
Schreiner, T., Lehmann, M., Rasch, B., 2015. Auditory feedback blocks memory benefits of cueing during sleep. Nat. Commun. 6, 8729.
Schreiner, T., Doeller, C.F., Jensen, O., Rasch, B., Staudigl, T., 2018. Theta phase-coordinated memory reactivation reoccurs in a slow-oscillatory rhythm during NREM sleep. Cell Rep. 25, 296–301.
Shimizu, R.E., Connolly, P.M., Cellini, N., et al., 2018. Closed-loop targeted memory reactivation during sleep improves spatial navigation. Front. Hum. Neurosci. 12, 28.
Simon, C.W., Emmons, W.H., 1956. EEG, consciousness, and sleep. Science 124, 1066–1069.
Simor, P., Steinbach, E., Nagy, T., et al., 2018. Lateralized rhythmic acoustic stimulation during daytime NREM sleep enhances slow waves. Sleep.

Staresina, B.P., Bergmann, T.O., Bonnefond, M., et al., 2015. Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep. Nat. Neurosci. 18, 1679–1686.
Sterpenich, V., Schmidt, C., Albouy, G., et al., 2014. Memory reactivation during rapid eye movement sleep promotes its generalization and integration in cortical stores. Sleep 37, 1061–1075.
Tempesta, D., Socci, V., De Gennaro, L., Ferrara, M., 2017. Sleep and emotional processing. Sleep Med. Rev.
Thair, H., Holloway, A.L., Newport, R., Smith, A.D., 2017. Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. Front. Neurosci. 11.
Tononi, G., Cirelli, C., 2003. Sleep and synaptic homeostasis: a hypothesis. Brain Res. Bull. 62, 143–150.
Tononi, G., Cirelli, C., 2014. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron 81, 12–34.
Tononi, G., Riedner, B., Hulse, B., Ferrarelli, F., Sarasso, S., 2010. Enhancing sleep slow waves with natural stimuli. Medicamundi 54, 73–79.
Vahdat, S., Fogel, S., Benali, H., Doyon, J., 2017. Network-wide reorganization of procedural memory during NREM sleep revealed by fMRI. eLife 6, e24987.
Van Dongen, E.V., Takashima, A., Barth, M., et al., 2012. Memory stabilization with targeted reactivation during human slow-wave sleep. Proc. Natl. Acad. Sci. U. S. A. 109, 10575–10580.
Walsh, J.K., Vogel, G.W., Scharf, M., et al., 2000. A five week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Med. 1, 41–49.
Wei, Y., Krishnan, G.P., Komarov, M., Bazhenov, M., 2017. Differential roles of sleep spindles and sleep slow oscillations in memory consolidation. bioRxiv 153007.
Weigenand, A., Mölle, M., Werner, F., Martinetz, T., Marshall, L., 2016. Timing matters: open-loop stimulation does not improve overnight consolidation of word pairs in humans. Eur. J. Neurosci. 44, 2357–2368.
Westerberg, C.E., Florczak, S.M., Weintraub, S., et al., 2015. Memory improvement via slow-oscillatory stimulation during sleep in older adults. Neurobiol. Aging 36, 2577–2586.
Whitehurst, L.N., Cellini, N., Mcdevitt, E.A., Duggan, K.A., Mednick, S.C., 2016. Autonomic activity during sleep predicts memory consolidation in humans. Proc. Natl. Acad. Sci. U. S. A. 113, 7272–7277.
Zelano, C., Sobel, N., 2005. Humans as an animal model for systems-level organization of olfaction. Neuron 48, 431–454.