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1   **Stimulating the sleeping brain: current approaches to modulating**
2   **memory-related sleep physiology**

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7   **RUNNING HEAD:** *Sleep and memory*
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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.

Keywords: closed-loop system; memory consolidation; non-invasive brain stimulation; pharmacological intervention; sleep; slow oscillations.

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 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 0.5–1Hz), thalamic sleep spindles (i.e., short oscillatory bursts of 9–16Hz originated in the reticular thalamus), and hippocampal sharp-wave ripples (SWR; transient and fast excitatory oscillations of about 200Hz 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 (9-12Hz) and fast (12-16Hz) 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, Tononi and Cirelli, 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 (8Hz) or fast (14Hz) 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 (0.5-4Hz) (Perl et al., 2016, Arzi et al., 2014) and slow spindle (9-12Hz) 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 (Figure 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).

Figure 1. Example of a targeted memory reactivation (TMR) paradigm. 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.

Figure 1. Example of a targeted memory reactivation (TMR) paradigm. **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.

TMR can be performed with different types of sensory stimuli. As mentioned in the previous paragraph, Rasch and colleagues (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 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 (1.5-4.5Hz) and parietal fast spindle (13-15Hz) 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 and colleagues (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 and colleagues (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 5Hz) 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 1500ms 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

1 show a lack of physiological responses (e.g., increased theta and spindles activity) to the auditory
2 cues during sleep (Cordi et al., 2018)

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

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

27 28 *2.2 Stimulating with non-meaningful sounds: Rhythmic and closed-loop auditory* 29 *stimulation*

30
31 Building on the limitations of the TMR approach and on the advancement of knowledge of
32 the physiology underlying memory processes during sleep, other methods have been developed
33 using stimulation during sleep with non-meaningful cues, such as rhythmic and closed-loop
34 auditory stimulation.

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

41 A couple of studies have recently attempted to use rhythmic sequences of acoustic stimuli
42 to enhance specific sleep oscillations. Ngo and colleagues tested the effect of either 0.8Hz or
43 random auditory stimulation (60 dB SPL, using in-ear headphones) with an inter-stimulus interval
44 (ISI) between 1.25s to 5s (Ngo et al., 2013a). They observed that the 0.8Hz stimulation increased
45 SO power after 10-15 minutes from the beginning of the stimulation compared to the random

1 stimulation and a sham condition. Moreover, the 0.8HZ stimulation induced more trains of SOs
2 during SWS compared to the other conditions.

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

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

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

25 These scientific advancements have led to the development of technological innovations in
26 which the delivery of sensory stimuli is triggered by specific sleep events, avoiding the timing
27 problems observed by the TMR and the rhythmic stimulation. In a seminal paper, Ngo and
28 colleagues (2013b) developed an auditory closed-loop feedback system able to detect online SO
29 activity and then deliver a brief auditory stimulation (i.e., 50-ms bursts of pink noise at 55 dB SPL)
30 during the SO up-state (Figure 2). This system was based on an adaptive amplitude threshold
31 method (with default value set at $-50\mu\text{V}$), and it was able to increase SO power, to boost spindle
32 activity phase-locked to the SO up-state and, remarkably, to increase memory performance in a
33 word-pair association task relative to a control condition. These findings were further replicated
34 in another study by the same group (Ngo et al., 2015). These papers opened the field to the idea
35 that sensory stimulation may be performed by targeting specific oscillatory events, allowing a
36 more precise control of the stimulation and the related outcomes. Following these papers, other
37 research groups have developed similar systems. Santostasi and colleagues (2015) created a system
38 based on a phase-locked procedure to predict the phase of a SO (of at least $-50\mu\text{V}$ of amplitude)
39 and to deliver a 50-ms pink noise stimulus in the transition from the down to the up state of the
40 SO. Of note, the sound had a volume ranging between 30 to 48 dB, based on individualized
41 auditory thresholds determined automatically by the system. With this system, they were able to
42 consistently target the SO at the 240° (with down phase at 90° and up phase at 270°). When they
43 applied this system to young (Ong et al., 2016) and older (Papalambros et al., 2017) adults to test
44 the effect at the physiological and behavioural level, using trains of 5 consecutive sounds separated
45 by 1.2s intervals, they observed an increase in SWA, which was associated with enhancements in
46 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 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.

Figure 2. Cartoon of an auditory closed-loop stimulation paradigm. The participant's 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).

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 $-75 \mu V$). When SOs were detected, the system delivered a 40ms 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 (Debellemanni 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 4s 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 and colleagues (2018) aimed to deliver a cue that resembled the frequency of each individuals' fast spindle (on average 13.4Hz) during the down-to-up phase transition (about 190ms 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., 50ms). Comparing this stimulation against an "arrhythmic" (seven clicks spaced by a jitter duration between 5 to 138ms) and a sham stimulation, they observed that both stimulations induced a delayed increased activity in fast spindles during the SO up phase (i.e., 500-1500ms 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, Ong et al., 2018). For example, Papalambros and colleagues (2017), comparing the EEG activity after stimulated and non-stimulated SOs, showed increased theta activity 500ms after the cue, and increased sigma activity after 1000ms 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 $-80\mu\text{V}$ 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 200ms 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 3s, 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 (0.5s after a spindle was detected) or later (2.5s 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 (Debellemanni et al., 2018)), and further investigations are required to clearly quantify the safety of these protocols over time.

3. Non-invasive brain stimulation (NIBS)

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

8 In 2004, Marshall and colleagues applied a specific tES, namely anodal transcranial direct
9 current stimulation (tDCS, Figure 3), with current constantly delivered at 0.75Hz (with current
10 density of 0.26 mA cm^{-2} applied in a 15s-on/15s-off fashion), during SWS (using F3 and F4 as
11 positive polarity sites and the mastoids as the reference), showing that the stimulation increased
12 declarative memory performance (i.e., word pairs task). At the physiological level, the stimulation
13 enhanced EEG activity below 3 Hz, reduced the EEG power in the 4-10 Hz range and the number
14 of spindles, compared to a sham condition. This result was further replicated by the same group in
15 a seminal paper using an anodal slow oscillatory tDCS (so-tDCS, Figure 3) with a sine wave of
16 0.75Hz, during NREM sleep (Marshall et al., 2006). In this latter study, the effect of the stimulation
17 was pronounced for frontal SOs (.5-1 Hz) and slow sigma frequency (8-12 Hz). Discrepancies
18 between these studies may be due to differences in the type of stimulation used. While in the first
19 study Marshall and colleagues use a “standard” anodal tDCS (i.e., the current is constant over time
20 and flows from the negative to the positive site), in the 2006 study they used an anodal so-tDCS
21 (i.e., a combination of DC and AC stimulation, with the current cyclically increasing and
22 decreasing in its intensity) applied for 5min on/1min off. Of note, to match the current intensity of
23 the first study, in 2006 Marshall et al. increased the current density to 0.517 mA cm^{-2} . Despite the
24 technical differences, both papers show electrical modulation of SOs resulting in post-sleep
25 memory benefit. However, the exact mechanism underlying this modulation is not still not well
26 understood. It is possible that the anodal stimulation, which is supposed to enhance the activity of
27 the stimulated area may have modulated SO activity by increasing the probability of action
28 potentials occurring in prefrontal regions, where SOs are generated (Murphy et al., 2009).

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

Figure 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)

Subsequent studies using similar protocols (i.e., 0.75Hz 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, Figure 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. (2016) findings using the same protocol but with a square wave instead of a sinusoidal oscillation (see also Figure 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 and colleagues (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 5Hz during SWS, (Garside et al., 2015, Marshall et al., 2011)). Of note, with the exception of Nitsche and colleagues (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 and colleagues (2016). They developed a feedback-controlled tACS system able to detect online sleep spindles during NREM and then to deliver a brief (about 1s) 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 and colleagues (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 0.16Hz or 0.24Hz). Although the authors reported an increase in the number of spindles in the first 2 hours 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 inpatients 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 and colleagues (2010) reported only minor effects on SWA after median nerve stimulation. Pereira and colleagues (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 0.75mg 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 and colleagues (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 (10mg), 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: 0.25mg/kg) and an AMPA receptor blocker (caroverine, 40mg) 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), 175mg), 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

1 REM sleep). The authors proposed that glutamatergic neurotransmission during sleep may be
2 involved in both synaptic potentiation (i.e., consolidation) and downscaling (i.e., forgetting). In a
3 recent pre-print, the same groups showed that DCS also facilitated the post-sleep encoding of new
4 declarative information (Asfestani et al., 2018).

5 The same group also tested the effect of pramipexole (0.5 mg), a D2 dopamine receptor agonist,
6 on overnight retention of pictures associated with low and high monetary reward, as well as in a
7 standard declarative and procedural task (Feld et al., 2014). Although the overall performance was
8 not affected by the drug, purportedly due to the induced suppression of SWS and REM sleep,
9 pramipexole affected the quality of performance: with decreased benefit of the high reward,
10 compared with placebo. Furthermore, Feld and colleagues (2016), tested the effect of intranasal
11 insulin, previously associated with enhanced memory encoding (Benedict et al., 2004, Benedict et
12 al., 2007), on overnight declarative and procedural consolidation, using an interference paradigm.
13 The authors showed that intranasal insulin (1.6ml insulin) affects sleep neurophysiology (i.e.,
14 increased growth hormone concentration and EEG delta activity) but it does not modulate memory
15 consolidation. However, this stimulation impaired the encoding of new material the following
16 evening, suggesting that intranasal insulin may impair the renormalization of synaptic weights
17 (Tononi and Cirelli, 2014), limiting the ability to learn new information.

18 In a series of studies that investigated the role of sleep spindles for hippocampal-dependent
19 memory consolidation, our group compared zolpidem, a GABA_A receptor agonist shown to
20 enhance sigma activity, and sodium oxybate, which interacts with the GABA_B receptor and has
21 conversely been shown to decrease sigma activity. Initially, we conducted a dose-response study
22 of zolpidem (5mg and 10mg) and sodium oxybate (2.5g and 3g) to determine the optimal dose of
23 zolpidem for increasing the density of N2 sleep spindles (Brunner et al., 1991, Feinberg et al.,
24 2000), and sodium oxybate for decreasing the density of N2 sleep spindles in an early morning
25 nap (Mednick et al., 2013). The nap occurred at 8:30 AM to capitalize on circadian fluctuations in
26 REM sleep (highest in the morning) and maximize differences in sleep stages between the drug
27 and placebo conditions. Next, we conducted a double-blind, placebo-controlled study comparing
28 the effect of three pharmacological interventions (10mg zolpidem, 2.5g sodium oxybate, and
29 placebo) on the consolidation of information from three memory domains: verbal, motor, and
30 perceptual. In line with prior studies, zolpidem increased sleep spindle density and decreased REM
31 sleep. At the behavioral level, zolpidem improved verbal memory but decreased perceptual
32 learning. However, no changes were found for motor learning across drug conditions. Verbal
33 memory performance was significantly correlated with spindle density in zolpidem and placebo,
34 and marginally in sodium oxybate. Interestingly, when spindle density was included as a covariate
35 in verbal memory analysis as a function of the drug, the main effect of drug condition disappeared,
36 while the spindle density effect on performance was highly significant. In a second study, we
37 compared the effect of zolpidem, sodium oxybate and placebo on memory for pictures that varied
38 across two dimensions: valence (positive, neutral and negative) and arousal (high and low). We
39 found that zolpidem increased memory for the negative and high arousal pictures significantly
40 more than placebo, suggesting that spindles may be involved with emotional memory more so than
41 REM sleep, which was not related to task performance (Kaestner et al., 2013).

42 Taken together, these results indicated that the verbal memory improvements with zolpidem
43 may represent an enhancement of a normal consolidation process during sleep since similar
44 correlations between spindles and verbal memory were found in all three drug conditions. In
45 addition, the experimental manipulation of spindles and the associated increase in verbal memory
46 raises the possibility that sleep spindles may represent physiological processes critical for

1 declarative verbal memory consolidation, evinced by the significant effect of spindles on
2 performance in the covariate analysis

3 It should be noted that long-term negative side effects may be expected for most of the
4 pharmacological interventions. For example, the dopamine agonists may increase the risk of sleep
5 attack but they can also augment the risk of developing sleep apnea (at least in patients with
6 Parkinson disease (Borovac, 2016)) and insomnia symptoms (Ruigt and van Gerven, 2018).
7 Similarly, drugs targeting the cholinergic system, due to their stimulant action, may impair sleep
8 architecture (Ruigt and van Gerven, 2018). For example, using a cholinesterase inhibitor (i.e.,
9 galantamine), Biard and colleagues (2015) showed that, compared to placebo, the administration
10 of the drug increases the proportion of REM, and reduced the latency and increased the proportion
11 of REM at the detriment of N3 sleep. It also induced a more fragmented sleep (higher WASO,
12 proportion of N1 and number of awakenings). Other studies showed that ketamine increases SWA
13 (at least in patients with major disorders), but this effect decreases over a few nights (Duncan and
14 Zarate, 2013). GABAergic drugs seem to induce few adverse effects, mildly impacting sleep
15 architecture, since they tend to boost the activity of endogenous GABA (Ruigt and van Gerven,
16 2018). Indeed, studies testing the effect of zolpidem in patients with insomnia showed positive
17 effects in reducing sleep onset and increasing N3 and sleep efficacy, without reporting any side
18 effects (Rummer et al., 1993, Walsh et al., 2000) (Rummer et al., 1993; Walsh et al., 2000).
19 However, zolpidem also showed a consistent decrease in REM sleep, which had subsequent
20 negative impact on perceptual learning (Mednick et al., 2013).

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

25 26 27 **6. A wearable future?**

28
29 Although most of the studies presented in this review were run in a laboratory setting, these
30 stimulation techniques may be potentially used in free-living conditions. An example is the study
31 by Debellemanni and colleagues (2018), who combined a wearable device for automated sleep
32 monitoring (Cellini et al., 2015) with a closed-loop system to deliver auditory cues, showing that
33 at-home stimulation may be feasible for several days and can produce positive outcomes (e.g.,
34 increased SWA). Acoustic stimulation during sleep, either in a closed-loop or rhythmic fashion,
35 seems to be the more feasible approach for free-living stimulation. Moreover, the developments in
36 wearable sleep trackers, which are able to detect peripheral signals such as heart rate and claims
37 to score sleep stage based on a combination of biosignals (de Zambotti et al., 2018), may give the
38 opportunity to use cardiac signals as a proxy of the sleeping brain, providing a reliable temporal
39 window for acoustic stimulation. Olfactory stimulation is more complex to conduct, but future
40 studies may provide new insights into how to conduct these stimulations at home (for example
41 using automated odor dispenser). The development of systems to perform odor stimulation in free-
42 living conditions may be particularly important, considering that odors have been shown to
43 modulate not only the consolidation of individual memories but also behaviors (Arzi et al., 2014,
44 Cellini and Parma, 2015). Also, olfactory stimulation may be advantageous for populations such
45 as individuals with autism spectrum disorder, who seems to be particularly sensitive to olfactory
46 information (Parma et al., 2013) At home tES stimulations may be potentially feasible, given the

1 portability of most of the equipment and the presence, on the market, of “over-the-counter”
2 devices. However, tES may induce several moderate adverse events and, although there are no
3 legal issues about using some of tES device at home without a clinical control, ethical aspects need
4 to be carefully taken into account (Antal et al., 2017). Similarly, pharmacological interventions for
5 treating sleep-dependent memory loss should be considered alongside all the potential caveats of
6 any pharmacotherapy engenders.

7 Overall, it is possible to imagine a near future in which different types of simulations are
8 performed during sleep using wearable devices. Although the speed that these devices will come
9 to market may outpace researchers ability to evaluate their reliability and safety, similar to the path
10 of wearable sleep trackers (de Zambotti et al., 2016). Therefore, researchers and companies alike
11 need to consider not only legal but also ethical aspects of modulating the sleeping brain (Cellini
12 and Parma, 2015). Lastly, it should be remarked that although some studies have tested the impact
13 of brain stimulation techniques on more ecological (i.e., navigation task in a virtual reality
14 environment, (Shimizu et al., 2018)) or more applied task (i.e., language learning, (Schreiner and
15 Rasch, 2017)), most of the studies examine effect on controlled and simple laboratory tasks.
16 Bringing these techniques in free-living conditions, to enhance or modulate real behaviors and
17 cognitive processes, can indeed be a challenge, and their beneficial effects can be less effective
18 than in a laboratory setting. Moreover, precautionary measures should be taken to avoid the use of
19 wrong stimulation protocols, which can induce negative consequences to the ongoing brain
20 activity, affecting several sleep functions. Lastly, current stimulation techniques are far from able
21 to be used in a therapeutic context. The few studies that have tried to use TMR with anxiety
22 disorders failed to show any clinical benefits for the patients (Rihm et al., 2016, Groch et al., 2017)
23 whereas there is a lack of data on the potential benefit of these techniques on sleep disorders
24 (Cellini, 2017). All in all, real-world application as a goal requires that researchers test the effect
25 of these techniques on more complex and ecological task.

26 27 28 **7. Conclusion**

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

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