Sleep and memory: mechanisms and implications for psychiatry

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Purpose of review
This review discusses current concepts on the relationship between sleep, memory formation and underlying neural refinements, with a particular focus on possible ways to use or modulate sleep in a targeted manner to augment psychiatric and psychotherapeutic treatments.

Recent findings
The most promising lines of research with regard to psychiatry and psychotherapy center on the targeted implementation or modulation of sleep to augment existing or create novel forms of treatment.

Summary
The modulation of sleep and interconnected neural plasticity processes provides a window of opportunity for developing novel treatments in psychiatry and psychotherapy.

Keywords
learning, memory, neural plasticity, sleep

INTRODUCTION

Who, some million years ago, amid an unfolding struggle for life, would have bet that a state of unconsciousness, inactivity and high vulnerability would become a bestseller of evolution? However, that exactly is what sleep has become. This indicates that sleep provides substantial advantages to animals and humans, potentially by allowing for continuous adaptation of central nervous system function to novel stimuli (plasticity), while keeping overall network function stable (stability).

MEMORY IS A FUNDAMENTAL CHARACTERISTIC OF ANIMALS AND HUMANS

The ability to acquire and consolidate new memories is a crucial for animals and humans. Beyond the acquisition of knowledge and skills, this ability is a prerequisite to experiencing ourselves as coherent entities in time and space. The physiological correlate of learning and memory formation is neural plasticity, that is, the ability of the developing but also of the adult brain to adapt its function and structure to a changing environment. Particularly important adaptions occur at the level of synapses – the contact points of electrical and chemical communication between nerve cells (synaptic plasticity). Within a continuous storm of electrical firing, joint neurons detect relevant information based on coincident (associative) activation, and encode this coincidence through a persistent strengthening of transmission across their synapses [associative synaptic plasticity; e.g., synaptic long-term potentiation (LTP) [1]], a key mechanism for memory formation.

SYNAPTIC REACTIVATION DURING SLEEP

Interestingly, new memory traces encoded during wakefulness experience an offline reactivation during sleep, which has been first shown with the aid of intracerebral recordings in animals [2] and brain imaging techniques in humans [3]. It appears that reactivation can occur during both major sleep states, that is nonrapid eye movement (NREM) and REM sleep. The active system consolidation

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KEY POINTS

- Sleep critically modulates basic processes of neural plasticity and memory formation.
- Sleep may be used or modulated in a targeted manner to augment existing or develop novel treatments in psychiatry and psychotherapy.

hypothesis, which has been originally elaborated for declarative memory, posits that during wakefulness new memories are transiently encoded into a temporary store, that is the hippocampus in the declarative memory system. During sleep, these memory traces are reactivated and redistributed for long-term storage in neocortical assemblies. This system consolidation is thought to emerge from a dialogue between the hippocampus and neocortex, driven by sharp-wave ripples in the hippocampus and thalamo-cortical sleep spindles – oscillations which are coordinated by depolarizing up-phases of neocortical slow oscillations during NREM sleep [4]. This reactivation is thought to promote the consolidation of initially fragile memories. In addition to the observance of reactivation, which suggests but not directly demonstrates a strengthening of novel memory traces, it has recently been shown in rodents that sleep promotes the formation of novel branch-specific synapses after learning, underlining the importance of sleep for the consolidation of previously encoded memories [5].

SYNAPTIC DOWN-SCALING DURING SLEEP

Recurrent potentiation of synapses during daytime wakefulness leads to a net increase in synaptic strength [6,7]. This net increase has important drawbacks, namely, a greater cellular demand for energy and supplies, an increase in volume, a lower signal-to-noise ratio in neural networks and, on the longer run, saturation. Over the past years, there is growing evidence that the maintenance of network stability is ensured by homeostatically driven global down-scaling of synaptic strength that predominantly occurs during sleep (synaptic homeostasis hypothesis [6,8]). This down-scaling of synaptic strength is thought to occur during slow-wave NREM sleep, which is characterized by oscillating firing patterns with phases of intense burst firing (ON periods) and phases of complete silence (OFF periods) in neural assemblies. This down-scaling has been proposed to be a vital function ensuring the brain's capacity to acquire new and relevant information. Along these lines, it is clear that the concept of generalized

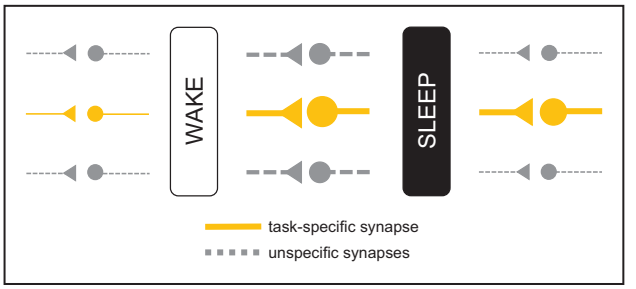

FIGURE 1. Model of sleep and synaptic plasticity. Synaptic LTP of a task-specific synapse (solid line) enhances its transmission efficacy and probability to activate the postsynaptic cell. However, intense postsynaptic cell firing also increases the probability of unspecific surrounding synapses (dashed line) to undergo LTP, resulting in an increase of global synaptic strength. During wakefulness, this runaway process results in higher cellular needs for energy and supplies, an increase of volume, a decrease of the signal-to-noise ratio and, on the longer run, results in saturation. Sleep is proposed to provide a fine orchestration of global downscaling of unspecific synapses and local strengthening or protection of task-relevant synapses. These processes are thought to keep the network plastic for information storage through adaption of synaptic weights, while at the same time assuring neural network stability. LTP, long-term potentiation.

down-scaling of all synapses has theoretical and empirical limitations. For instance, it is not compatible with the existence of long-term memories that, despite not being actively used, persist over decades. To date, there is an important debate of whether variations of down-scaling, such as a down-selection of weak synapses sparing the strong ones, characterize sleep, or whether this process is complemented by processes of local synaptic strengthening, for example through reactivation during sleep [6,9,10▪]. In this discussion, it is likely that both processes – although opposite in direction – co-occur finely orchestrated during sleep (Fig. 1).

Apart from global down-scaling of synaptic strength to maintain neural network stability, the targeted depotentiation or erasure of synapses – in the sense of targeted forgetting – is recently discussed, as it is thought to be necessary for incorporating novel information into established schemata or for gist abstraction [11▪]. This process has been proposed to be unique to sleep and of particular importance for the experience-dependent reshaping of synaptic circuits not only in the developing, but also in the adult brain. Chronic or temporary deficits in this process may result in various intellectual or developmental disabilities (e.g. autism-related failures to prune) and mental health problems (e.g. posttraumatic stress disorder [11▪]).

SLEEP PROMOTES MEMORY CONSOLIDATION

In line with these neural models, compared to equal periods of wakefulness, sleep has been shown to promote the consolidation of declarative (knowledge or memory episodes that can be verbalized, e.g. vocabulary or word associations) and nondeclarative (skills and procedures that are usually difficult to verbalizes, e.g. playing the piano) memories on a behavioral level [12]. Experimentally difficult to control for and therefore not yet fully resolved is the question as to what extent sleep-specific brain activity patterns, in contrast to a mere reduction to interference (interfering sensory input or motor activity), or circadian processes, contribute to the observed increase in memory consolidation across periods of sleep [13–15]. Patients with chronic insomnia or sleep apnea show impaired sleep-related memory consolidation compared to healthy sleepers [16–18]. At present, it is unclear if improvement of sleep through treatment in these cohorts would result in improved sleep-related memory formation. It is important to note that hypnotics that are frequently prescribed to treat insomnia and increase sleep duration, including benzodiazepines and benzodiazepine receptor agonists, significantly impair synaptic plasticity in animals [19] and memory formation in animals and humans [20]. This pharmacologically induced dissociation of sleep duration and sleep function, along with several other lines of argument, further supports the implementation of cognitive behavior therapy as the first-line treatment for chronic insomnia.

IMPLEMENTING SLEEP TO PROMOTE MEMORY AND PLASTICITY

A current field of research addresses the question if sleep can be used in a targeted manner to promote memory formation and underlying neural plasticity. Indeed, the insertion of an additional short period of daytime sleep has been shown to strengthen previously encoded memory traces [21,22]. However, the assessment of behavioral data is always prone to confounding variables and alternative explanations (e.g. attentional or motivational aspects). For example, in motor learning, it is difficult to disentangle a sleep-dependent strengthening of trained motor memory traces from an enhanced alleviation of on-task fatigue accumulated during prior motor practice [23]. In a recent study in healthy participants, we used a transcranial magnetic stimulation (TMS) protocol, that is paired associative stimulation, to noninvasively induce LTP-like plasticity in the human cortex and to better control for the above mentioned confounding factors. Our results suggest an increased consolidation of this form of plasticity after a daytime nap compared to an equal period of wakefulness, demonstrating the importance of sleep in promoting the consolidation of LTP-like plasticity (Maier *et al.*, unpublished data). Other work centers on the restorative role of intermediate sleep interventions on learning and performance. For instance, the deterioration of performance on a visual discrimination task can be prevented by a subsequent period of slow-wave sleep but not by an equal period of active or passive wakefulness (Nissen *et al.*, unpublished data; [24,25], but see [15]). Furthermore, the acquisition of novel episodic memories was impaired after a period of extended wakefulness and restored after nighttime sleep or an intermediate short period of daytime sleep in healthy humans [26,27]. The restorative aspect of sleep is further supported by own previous work, showing an intact inducibility of LTP-like plasticity in the human cortex after regular nighttime sleep, but an occlusion after extended wakefulness [28▪]. Both aspects (i.e. memory consolidation and restorative processes) are critically important for daily life activities and of particular relevance in fields of high-level performance, such as professional sports and music or demanding work tasks (e.g. aviation). With respect to potential clinical applications, first studies suggest that the efficacy of a psychotherapeutic intervention (exposure therapy) can be boosted by targeted periods of sleep after the psychotherapeutic intervention [29,30].

MODULATING SLEEP TO PROMOTE MEMORY AND PLASTICITY

In terms of modulating sleep, initial studies provide proof-of-concept for a strengthening of select memories through stimuli-cued reactivation during NREM slow-wave sleep. This has been shown for odor-cues, tone-cues or word-cues that were coupled with memory acquisition during wakefulness and later re-exposed during sleep [31–34]. Other studies report the promotion of sleep-dependent memory consolidation by the increase of NREM slow oscillations with sensory stimuli, transcranial direct-current stimulation or TMS [35]. This may open a window for targeted reactivation and consolidation of information that has previously been encoded in psychotherapeutic interventions. In turn, current own work follows the idea that a selective suppression of slow oscillations might induce well-documented therapeutic effects of sleep deprivation in patients with major depressive disorder (‘sleep deprivation light’, [36]). Here, therapeutic sleep deprivation or, maybe, select

slow-wave suppression might correct a deficient upscaling of overall synaptic strength (homeostatic plasticity) and lead to a shift into a more favorable window of associative synaptic plasticity in patients with major depression [36,37].

SLEEP AND MEMORY REORGANIZATION

In addition to the veridical storage of information, our memory system is characterized by a qualitative reorganization of memory content. This means that our brain is not very likely to store information as an exact representation, but it rather reconstructs and adapts new information in the light of already existing schemata. Some studies suggest that sleep, and especially REM sleep, can promote diverse forms of memory reorganization, such as generalization [12,38]. This view has gained attention in the last years with respect to the disintegration or recombination of the emotional tone of newly acquired memories [39]. Especially, the unbinding of a specific memory content from its emotional envelope during sleep is promising in the psychiatric field of mood or anxiety disorders. As mental disorders are frequently accompanied by disrupted sleep, including disruptions of REM sleep, these sleep disruptions may impair the adequate organization of memories, particularly in terms of emotional memories, which may either facilitate the onset or worsen the time course of the disorder. Furthermore, sleep disruptions may prevent novel health-related information (e.g. acquired during psychotherapeutic treatment) to be integrated in pre-existing schemata, which may maintain mental distress. However, despite the appealing character and some neurobiological plausibility, the results, to date, are inconsistent ([40], overview [41]) and this area of interest needs further investigation.

CONCLUSION

There is an increasing body of evidence that sleep plays a pivotal role in the orchestration of neuroplasticity. Further research into sleep and plasticity is expected to inform about the neural basis of healthy functioning and mental disorders and may open a window for augmenting existing or developing novel treatments in psychiatry and psychotherapy.

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