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Sculpting memory during sleep: concurrent consolidation and forgetting

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There is compelling evidence that sleep actively supports the formation of long-lasting memory representations. Experimental cuing of memories proved that neural replay of representations during sleep plays a causal role for this consolidation, which has also been shown to promote neocortical synaptic plasticity and spine formation. Concurrently, sleep has been proposed to facilitate forgetting through processes of synaptic renormalisation. This view received indirect support by findings in humans of sleep enhancing TMS-evoked plasticity and capabilities for encoding new information. First direct behavioural evidence of sleep inducing forgetting has only recently emerged after encoding large amounts of stimuli in adults. We propose forgetting complements sleep-dependent consolidation and facilitates gist abstraction especially at high memory loads, when reactivation-based consolidation reaches capacity limits.

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Introduction

The formation of long-term memory relies on the two distinct processes of encoding (or learning) and consolidation. Retrieval is a third process that contributes to memory formation by re-instating the stored information. Between encoding, that is the uptake of the information, and retrieval lies the period of retention, and already at the beginning of modern memory research it was proposed that during this retention period memories are not merely passively stored but that an active process of consolidation occurs [1], which has received wide support over the past century [2]. Especially, the idea that memory is consolidated during the brain's offline periods of deep slow wave sleep has risen to a champion of consolidation theory (Figures 1 and 2) [3–5]. Just recently, in the neocortex, the formation of dendritic spines was observed , during sleep after learning a motor task, as a neural substrate of memory formation, which was positively related to task performance [6••].

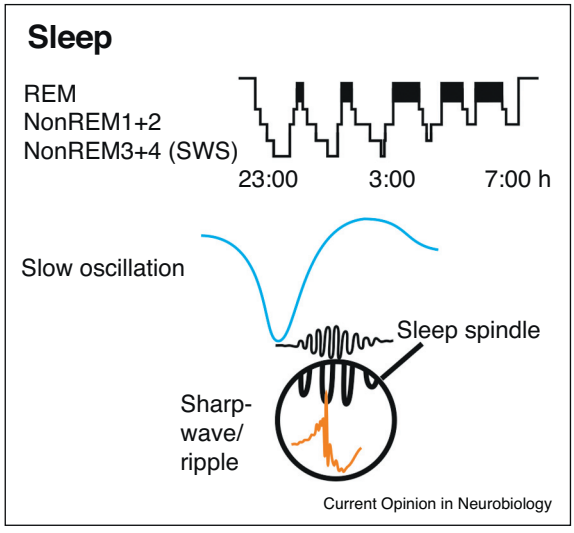
At its outset, memory research mainly focused on forgetting [7]. Essentially, two forms of forgetting were proposed. The first argues that forgetting occurs due to interference, that is older memory traces are constantly being overwritten by newer encoding events. Consequently, a passive role of sleep protecting from interference has been claimed repeatedly since its first conceptualisation [8], even though this type of forgetting seems to play only a minor role for memories involving the hippocampal system [9]. The second claims that memory traces passively decay over time and this account, later on, was extended to include *active* decay processes [10]. Here also, sleep has been proposed to play a major role, renormalizing synaptic weights and balancing out potentiation occurring as a result of encoding information during wake (Figure 2) [11••].

Covering mainly the period from 2013 to now, we review the latest developments regarding sleep's role for consolidation and forgetting. Initially, it seems difficult to reconcile these two accounts. To the contrary, building on our previous reasoning [4,12] we will present a framework, derived from novel developments in the field, to explain how consolidation and forgetting work together to sculpt lasting memories from a day's clay of episodic experiences. Ultimately, forgetting might arise as the fourth process of memory formation that enables the long-term function of the other three processes.

Strengthening memory during sleep

The hypothesis that during sleep memory benefits from the repeated replay of neuronal representations that were formed to encode information during prior wakefulness was induced from the initial finding that in rats hippocampal place cells that show correlated firing during wake encoding of a simple maze re-exhibit this correlated firing pattern during subsequent slow wave sleep (SWS) [13] and replay during sleep has recently been shown to predict reinstatement strength during retrieval [14]. This

Figure 1



Sleep stages and oscillations. Sleep and memory research has greatly benefited from the identification of discrete sleep stages and associated oscillatory phenomena. Rapid eye movement (REM) sleep, which occurs mainly during the second half of the night, is characterised by wake-like desynchronized low amplitude EEG, which in the past made it the foremost candidate for sleep-dependent memory processing. To the contrary, reprocessing of memory representations has been shown to occur mostly during deep nonREM sleep (also slow wave sleep—SWS), which is most abundant during the first half of the night and is characterized by high-amplitude low-frequency oscillations (~0.75 Hz slow oscillations) in the surface EEG. NonREM sleep coordinates memory replay by locking hippocampal sharp-wave/ripples, which enwrap the replayed memory information, to the excitable troughs of the thalamo-cortical sleep spindle. The spindle itself is phase-locked to the up-state of the neocortical slow oscillation, thereby ensuring that the reactivated information reaches the neocortex during the excitable up-state of the slow oscillation. This process is supported by the specific neuromodulatory milieu of NonREM sleep that enables information flow from the hippocampus to the neocortex, including low levels of cortisol and acetylcholine.

research was extended to show that sequences of place cells that are replayed in the hippocampus are coordinated with replay of the sensory cortex [15] and of grid cells in the entorhinal cortex [16]. In fact, this replay can be evoked by targeted memory reactivation, that is by re-presenting a cue (*e.g.* an odour or a sound) that was present during encoding again during SWS after encoding [17]. Correspondingly, in rats re-presenting a sound that predicted the correct choice in a spatial learning paradigm during sleep after learning led to the re-emergence of the associated firing pattern of place cells [18••]. In humans, reactivating memory during sleep by re-presenting auditory cues from a Dutch–German paired associate paradigm learned before sleep enhances memory for the cued pairs [19]. In fact, this type of targeted memory reactivation can even be used to reduce notoriously persistent race and gender stereotypes [20] and to enhance the extinction of conditioned fear responses [21].

During NonREM sleep an intricate interplay of oscillations, that is neocortical slow oscillations (0.5–1 Hz), sleep spindles (12–16 Hz) originating from thalamus, and hippocampal sharp-wave/ripple complexes, occurs that can be measured with extracranial and intracranial EEG and which is thought to coordinate consolidation. Using intracranial EEG electrodes, in human epileptic patients, it was shown that the neocortical slow oscillation groups sleep spindles to its excitable up-state and that sharp-wave/ripples in turn are grouped to the spindle throughs and vice-versa [22•,23]. Importantly, high gamma in the cortex has also been shown to be nested in spindle troughs in mice [24]. The efficacy of the slow oscillation to enhance memory consolidation was demonstrated in humans using closed-loop auditory stimulation. In this experiment, short bursts (50 ms) of pink noise were presented during SWS timed to the slow oscillation up-state, which effectively induced high-amplitude slow oscillatory activity with spindle power phase-locked to the up-states [25•]. Interestingly, driving slow oscillatory events further by stimulating extended trains did not further enhance sleep spindles, indicating a self-limiting process [26]. Similarly, boosting sleep spindles by transcranial alternating current stimulation can improve motor memory consolidation [27] and electrically blocking ripples during sleep impairs memory consolidation [28]. Importantly, it seems to be the fine-tuned phase-locking of these different frequencies that makes consolidation during NonREM sleep possible [29]. In fact, enhancing slow oscillations pharmacologically by increasing GABAergic tone does not enhance memory consolidation, as simultaneously slow oscillation to sleep spindle phase-amplitude coupling is disrupted [30].

In addition to oscillatory prerequisites, NonREM sleep also offers a unique neurochemical pattern enabling consolidation, as low levels of cortisol and acetylcholine are essential to promote the hippocampal-to-neocortical dialogue [31–34]. Reward related signals also seem to play a major role, as dopaminergic activity during encoding enhances replay during subsequent sleep [35•]. Moreover, replay activity during sleep has been shown in reward related areas such as the ventral striatum [36] and the ventral tegmental area [37]. Enhancing dopaminergic neurotransmission pharmacologically during sleep in humans enhances the consolidation of low rewarded items to match high rewarded items [38]. However, it is still unclear, if plastic processes assumed to be induced by neural replay activity during sleep, are equivalent to those active during wakefulness. For example, blocking AMPA or NMDA receptors during sleep does not impact consolidation in humans [39]. It might turn out that during sleep direct electrical coupling between neurons via gap junctions is essential (GB Feld *et al.*, unpublished), which would fit well to the importance of oscillatory coupling for sleep-dependent memory consolidation.