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Review article

Offline neuronal activity and synaptic plasticity during sleep and memory consolidation

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ABSTRACT

After initial formation during learning, memories are further processed in the brain during subsequent days for long-term consolidation, with sleep playing a key role in this process. Studies have shown that neuronal activity patterns during the awake period are repeated in the hippocampus during sleep, which may coordinate brain-wide reactivation leading to memory consolidation. Consistently, perturbation of this activity blocks the formation of long-term memory. This 'replay' of activity during sleep likely triggers plastic changes in synaptic transmission, a cellular substrate of memory, in multiple brain regions, which likely plays a critical role in long-term memory. Two forms of synaptic plasticity, potentiation and depression of synaptic transmission, are induced in parallel during sleep and is termed "offline synaptic plasticity", as opposed to the "online synaptic plasticity" that occurs immediately following a memory event.

1. Introduction

The ability to retain and recall learned memories over time is a critical function that shapes our daily behaviors. Disruption to these processes occurs in various neurological and neuropsychiatric disorders, leading to alterations in memory performance. It is therefore important to elucidate the mechanism of memory formation both from basic scientific as well as clinical standpoints, to provide insight that might lead to the development of future therapies.

Sleep has long been implicated in memory (Gais and Born, 2004), with multiple studies reporting the importance of sleep in the long-term storage of memory and supporting the underlying cellular mechanisms. Studies in sleep deprived animals, achieved by continually disturbing the animal (Arthaud et al., 2015), result in memory impairments, though it is important to note that stress may also contribute to the observed phenotypes (Born and Gais, 2001; Galvao Mde et al., 2009). Subsequently, the discovery of the phenomena termed replay of neuronal activity led to a number of mechanistic studies on the relationship between sleep and memory (Kudrimoti et al., 1999; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994). During sleep, activity patterns that previously occurred during the awake period, replayed repeatedly during sleep in temporally compressed fashion. Concomitantly, the activity extends out to other cortical areas, observed as slow-wave spindles. Accumulating evidence shows that such brain-wide reactivation during sleep correlates with the memory formation. (Bendor and Wilson, 2012; Dupret et al., 2010; Girardeau et al., 2017; Lansink et al., 2009; Nakashiba et al., 2009; Siapas and Wilson, 1998; Singer and Frank, 2009). Therefore, replay event is widely considered as a critical substrate for the formation and retention of long-term memory.

On the other hand, synaptic plasticity such as long-term potentiation (LTP) and depression (LTD), a cellular counterpart of memory (Hayashi, 2022; Sakaguchi and Hayashi, 2012) have been implicated during sleep, following learning. While multiple studies have demonstrated the depression of synaptic transmission during sleep in broad areas of brain (Klinzing et al., 2019), the potentiation of the transmission has been also postulated to occur during hippocampal reactivation and sleep (Frankland and Bontempi, 2005). Recent advances in optogenetics and imaging methods have made it possible to examine the role of synaptic potentiation and depression *in vivo* during sleep with a high spatio-temporal resolution (Abdou et al., 2018; Goto et al., 2021; Hayashi-Takagi et al., 2015; Miyamoto et al., 2021; Nabavi et al., 2014). In this review, we will highlight these recent studies and advances in our understanding of synaptic plasticity during sleep in the hippocampus

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and cortex.

2. Memory consolidation

Memory is broadly classified into two distinct branches, declarative and procedural. While procedural memories such as motor skills or habitual behaviors are formed mostly unconsciously, declarative memories are the conscious recollection of episodic information, such as events and associated scenery (episodic memory) and semantic information, such as facts (semantic memory), that can be verbally stated and recalled (Squire and Dede, 2015). Episodic memories are initially formed and stored in the hippocampus, but are then transferred over time to other brain regions including cerebral cortex, in a process, called systems memory consolidation (Goto, 2022). This should not be confused with the synaptic memory consolidation where a synapse becomes more stable after plastic changes and less labile to reversal stimulation over time. In this review, we will discuss systems memory consolidation, which we will simply refer to as memory consolidation.

The idea of memory consolidation was first reported as early as the 19th century by Ribot, a French psychologist, who reported that new memories are more easily lost than old memories, as a result of brain damage (Frankland and Bontempi, 2005; Gilboa and Moscovitch, 2021; Ribot, 1882). Decades later, this idea was more comprehensively studied in patient H.M., who had large portions of his medial temporal lobes, including the hippocampus, removed bilaterally as an experimental treatment to control his intractable epilepsy (Corkin, 2002; Squire et al., 2004). Following the surgery, he had a deficit in the ability to form new declarative memories (Scoville and Milner, 1957). In addition, H.M. could not recall memories of the time immediately prior to the surgery. On the contrary, he retained memories from his childhood and maintained the ability to learn new motor skills, such as a mirror tracing task (Milner, 1962). Subsequent rodent experiments employing a range of memory dependent tasks supported the importance of the hippocampus in recent memory. They consistently showed that when hippocampal activity is disrupted, recent memory (memories up to several days after the training) retrieval is impaired, but remote memory retrieval remains intact (Anagnostaras et al., 1999; Kitamura et al., 2017; Takehara et al., 2003; Tse et al., 2007), although the impact of the hippocampal inhibition on remote memory retrieval varies depending on the type of experiment (Goshen et al., 2011; Sutherland et al., 2008). These studies suggest that memory is not a single process and that the hippocampus may have a time-limited role in associative fear memories evoked by polymodal contexts (Kim and Fanselow, 1992).

As memory gradually becomes less hippocampal dependent over time, it becomes more dependent on other brain regions outside the hippocampus. To identify the location of long-term memories, local levels of glucose metabolism were measured using tissue uptake of ^{14}C-2-deoxyglucose as an index of neuronal activity, resulting in identification of brain regions activated by recall of remote memory (Bontempi et al., 1999). This study identified several cortical regions with higher activity in memory recall 25 days after learning, compared to 5 days after learning. Among the cortical regions identified, selective inactivation of anterior cingulate cortex by local infusion of lidocaine, a local anesthetic, prevented the recall of remote memory but not recent memory, indicating that the reactivation of this region is required for memory recall (Frankland et al., 2004). Recent studies carried out more comprehensive mapping of neurons reactivated by memory recall by using c-fos, an activity-induced immediate early gene product (Roy et al., 2022). They demonstrated that a whole host of brain regions including both cortical and subcortical areas, were reactivated by remote memory recall. Additionally, using an optogenetic method to reactivate the neurons in these regions they were able to elicit memory-related behavior, suggesting that the remote memory is distributed widely across multiple brain regions.

3. Hippocampal-dependent memory consolidation during sleep

A well-known model of memory consolidation is the two-step consolidation theory (Buzsáki, 1989; Girardeau and Lopes-Dos-Santos, 2021; Sadowski et al., 2016). First, a population of hippocampal neurons fire when a memory-forming event occurs, resulting in the formation of cell assemblies that encode the experience. Then, during subsequent sleep, these cell assemblies spontaneously reactivated, thereby strengthening their binding through Hebbian LTP mechanisms and stabilizing memory traces.

Sleep can be broadly classified into the two distinct states, REM (rapid eye movement) and non-REM sleep. During non-REM sleep, hippocampal place cell activity that previously occurred during spatial exploration is repetitively replayed without sensory input (Skaggs and McNaughton, 1996). Such event-specific reactivation of hippocampal activity, occurs during brief bursts (~200 ms) and is associated with high-frequency (100–250 Hz) activity in the local field potential called sharp-wave ripples (SWRs) (Kudrimoti et al., 1999) (Fig. 1A). During replay, sequences of neurons that previously fired during an event (for example, running on a track) and may originally have spanned seconds to minutes, are temporally compressed down to the brief duration of a SWR.

This replay of neuronal activity following learning has attracted much attention as a possible mechanism, that could explain hippocampal-dependent memory consolidation during sleep (Girardeau and Lopes-Dos-Santos, 2021) (Fig. 1B). Consistent with this, it has been shown that offline neuronal activity in the hippocampus is required for the memory consolidation (Riedel et al., 1999; Shimizu et al., 2000). Studies examining cellular activation using immediate-early gene (IEG) products found reactivation of neural activity in the hippocampus after animals were returned to their home cages and allowed to sleep (Nakayama et al., 2015; Ribeiro et al., 1999). These observations suggest that reactivation of the hippocampus is important during the subsequent offline period of a memory task.

Indeed, there is considerable evidence implicating SWRs in the learning process. The strength of SWRs and subsequent memory performance are correlated (Dupret et al., 2010; Nakashiba et al., 2009). Arousal and attention also appear to play a role, with information that is more cognitively engaging being replayed more frequently (Bendor and Wilson, 2012; Singer and Frank, 2009). A recent calcium imaging study tracked the activity of memory-bearing cells (so called engram) during sleep (Ghandour et al., 2019). They found that several sub-ensembles composed of a single engram population, collectively fired during learning, with the same population of neurons preferentially reactivating during the subsequent sleep (Ghandour et al., 2019). The causality of SWRs in memory has been demonstrated by studies which disrupted replay, by either electrically or optogenetically terminating SWRs after learning, leading to memory impairment (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009; Jadhav and Frank, 2009; Norimoto et al., 2018). Furthermore, the disruption of SWRs has been shown to prevent reactivation of hippocampal assemblies upon re-exposure to the same environment (van de Ven et al., 2016). Together, these works suggest that reactivation of memory traces containing novel information during SWRs in non-REM sleep, is essential for memory consolidation.

Simultaneous electrical recording from multiple areas during non-REM sleep revealed the interaction among brain regions during memory consolidation. In particular, SWRs in the hippocampus are temporally correlated with slow-wave spindles recorded in the medial prefrontal cortex (mPFC) (Siapas and Wilson, 1998). This coordination of activity between the hippocampus and cortex is assumed to underlie communication between the two structures (Qin et al., 1997), in addition to other cortical areas (Hoffman and McNaughton, 2002) during memory consolidation. Such inter-regional communication during sleep stabilizes memories within the cortex and ultimately leads to them becoming independent of the hippocampus (Fig. 1B) (Frankland and Bontempi, 2005). While these studies were conducted in rodents, many

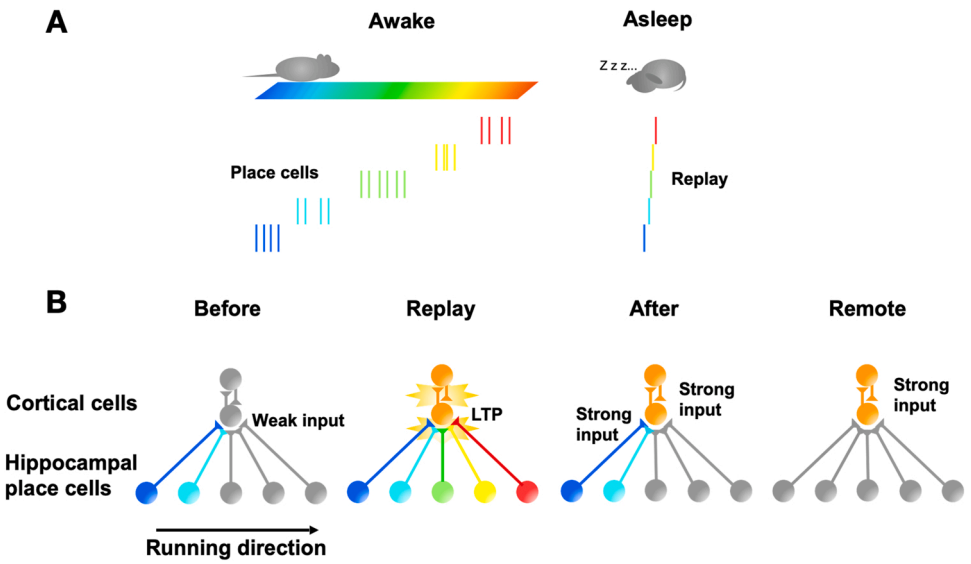

Fig. 1. Hippocampal replay and memory consolidation, (A) When an animal moves along a track, place cells sequentially fire. The same activity pattern is replayed at a much faster time scale during non-REM sleep, (B) During replay, activation of convergent inputs induces LTP at hippocampal-cortical synapses, as well as those within cortex. Following this, cortical neurons can fire even with a partial hippocampal input, or even in the absence of hippocampal activity.

of the same mechanisms have been observed in humans, with activity in the hippocampus and cortical areas becoming coordinated during SWRs (Skelin et al., 2021). Further, human functional MRI studies have revealed the visual content of dreams during the onset of non-REM sleep, represents the same neural substrate that is observed during awake periods (Horikawa et al., 2013), suggesting that the reactivation of learnt information also occurs in the human cortex during sleep. The direct causality of human cortical slow waves during sleep in memory consolidation was shown by transcranial magnetic stimulation (TMS) to increases the cortical slow oscillations during non-REM sleep in the frontal cortex, resulting in enhanced memory retrieval the following day (Marshall et al., 2006).

Coordinated activity across multiple brain areas during non-REM sleep is observed not only between hippocampus and cortex, but also between hippocampus and other brain regions. For example, spatial information in the hippocampus is reactivated in association with emotional information in the ventral striatum (Lansink et al., 2009), with place cells in reward locations firing shortly before reward-encoding neurons in the ventral striatum. This was observed during sleep SWRs after the rewarded experience and likely contributes to memory consolidation. Similarly, coordinated reactivations between the hippocampus and basolateral amygdala (BLA) have also been documented during non-REM sleep following training, but not before (Girardeau et al., 2017). Together, these results suggest that hippocampal replay during sleep coordinates reactivation in a wide range of brain regions during the consolidation of hippocampus-dependent memories.

Although the role of REM sleep in memory consolidation is less clear, several studies point to its role in memory. Replay is also observed during REM sleep, although unlike SWR-associated replay during non-REM sleep which occurs in a highly temporally compressed fashion, here activity is replayed at the much less compression (Louie and Wilson, 2001). It has also been shown that during transient increases in theta during REM sleep, referred to as phasic REM, coordination between CA3 and CA1 is enhanced, leading to increased synchronization in hippocampal circuits (Montgomery et al., 2008) together with modulation of hippocampal-cortical interactions (de Almeida-Filho et al., 2021). Experimental evidence to demonstrate the importance of REM sleep comes from the optogenetic manipulation of adult-born neurons in the dentate gyrus during REM sleep, which leads to impairment of contextual fear memories (Kumar et al., 2020). Further study investigating synaptic plasticity occurring in specific subpopulations of neurons and behaviors may lead to a better understanding of the function of REM sleep during memory consolidation.

4. Synaptic plasticity

Studies using either pharmacological or genetic approaches have demonstrated that LTP is required for learning. Blockade of hippocampal LTP by prior infusion of the NMDA-type glutamate receptor (NMDAR) antagonist AP5 into the rat hippocampus, significantly impaired spatial learning (Morris et al., 1986). A similar result was obtained with a hippocampal CA1-specific knockout of the NR1 subunit of NMDAR (Tsien et al., 1996). It has also been shown, that a potentiation of synaptic transmission can be induced by learning, similarly to the LTP that is induced in brain slices by high-frequency stimulation (Whitlock et al., 2006). Finally, it has been demonstrated that optogenetic induction of LTP can mimic context specific memory, while LTD can erase previously formed memories (Abdou et al., 2018; Nabavi et al., 2014). Together, these results indicate that synaptic plasticity in the hippocampus is essential for the acquisition of spatial memory.

One drawback common to both pharmacological and genetic studies is that they lack sufficient spatiotemporal resolution to identify synapses undergoing plastic changes, at either the cellular or synaptic level. Recently, a new optogenetic tool that allows for selective erasure of LTP have been developed (Fig. 2A) (Goto et al., 2021). This is based on the observation that an actin cytoskeletal regulating protein, cofilin (CFL), specifically accumulates at synapses that underwent LTP and enlarges dendritic spines (Bosch et al., 2014). The technique was developed by fusing CFL with a photosensitizer protein SuperNova (SN), which produces reactive oxygen species upon exposure to specific wavelength of light and inactivates molecules nearby, a method termed chromophore-assisted light inactivation (CALI) (Takemoto et al., 2013). Using CALI, CFL can be optically inactivated at any given timepoint, in a genetically defined neuronal population. In hippocampal neurons, CALI of CFL leads to a reversal of both the structural enlargement of dendritic spines induced by LTP (structural LTP or sLTP), as well as the associated potentiated transmission. The time-window of intervention using CALI is 30 min post LTP induction, after which other molecules start playing more significant roles in maintaining the enlarged synaptic structure. Since CFL accumulation is restricted to spines where LTP is induced, inactivation of CFL by CALI, selectively cancels LTP without affecting

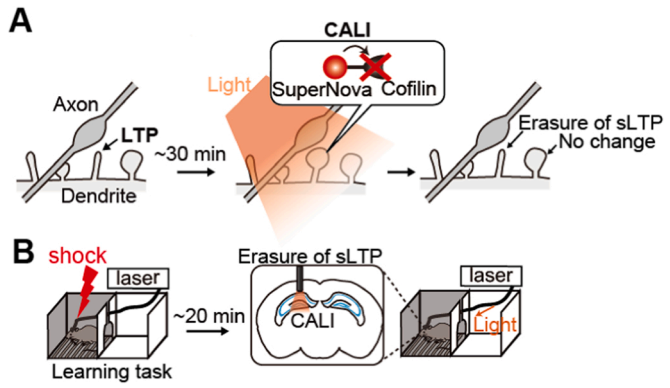

Fig. 2. Optical erasure of sLTP and specific memory, (A) An optical method for erasing structural LTP (sLTP) using CALI (Goto et al., 2021). Illumination on the spine expressing a fusion protein of CFL-SN induces CALI and inactivates CFL. Since CFL is highly accumulated in the spine that undergoes sLTP, illumination of the fusion protein specifically erases sLTP. sLTP is erased by CALI within 30 min of its induction; thus, this method enables spatiotemporal analysis of LTP, (B) In vivo erasure of sLTP. Task-associated memory was specifically erased by CALI in hippocampus within 20 min after shock.

basal synaptic transmission. Additionally, although CFL is involved in LTD (Zhou et al., 2004), under the conditions tested, CALI of CFL left LTD intact (Goto et al., 2021), possibly reflecting the difference in the mode of action of cofilin under these two different forms of synaptic plasticity. By expressing CFL-SN in CA1 of the mouse hippocampus and locally illuminating within 20 min after the training for an inhibitory avoidance task, the memory was erased, indicating that hippocampal LTP is induced immediately after a memory dependent task (Fig. 2B).

5. Hippocampal synaptic plasticity during sleep and memory consolidation

Two main hypotheses have been proposed for the synaptic mechanisms underlying the effects of sleep on memory. One is that sleep consolidates memory by further strengthening the synaptic connections that have been enhanced by learning. This is called active memory consolidation (Klinzing et al., 2019). On the other hand, the synaptic homeostasis hypothesis, posits that the role of sleep is to promote global synaptic downscaling, but that recently activated synapses are spared, because synapses coherently reactivated during sleep are protected (Tononi and Cirelli, 2014).

During sleep, the cell assemblies spontaneously replay, thereby

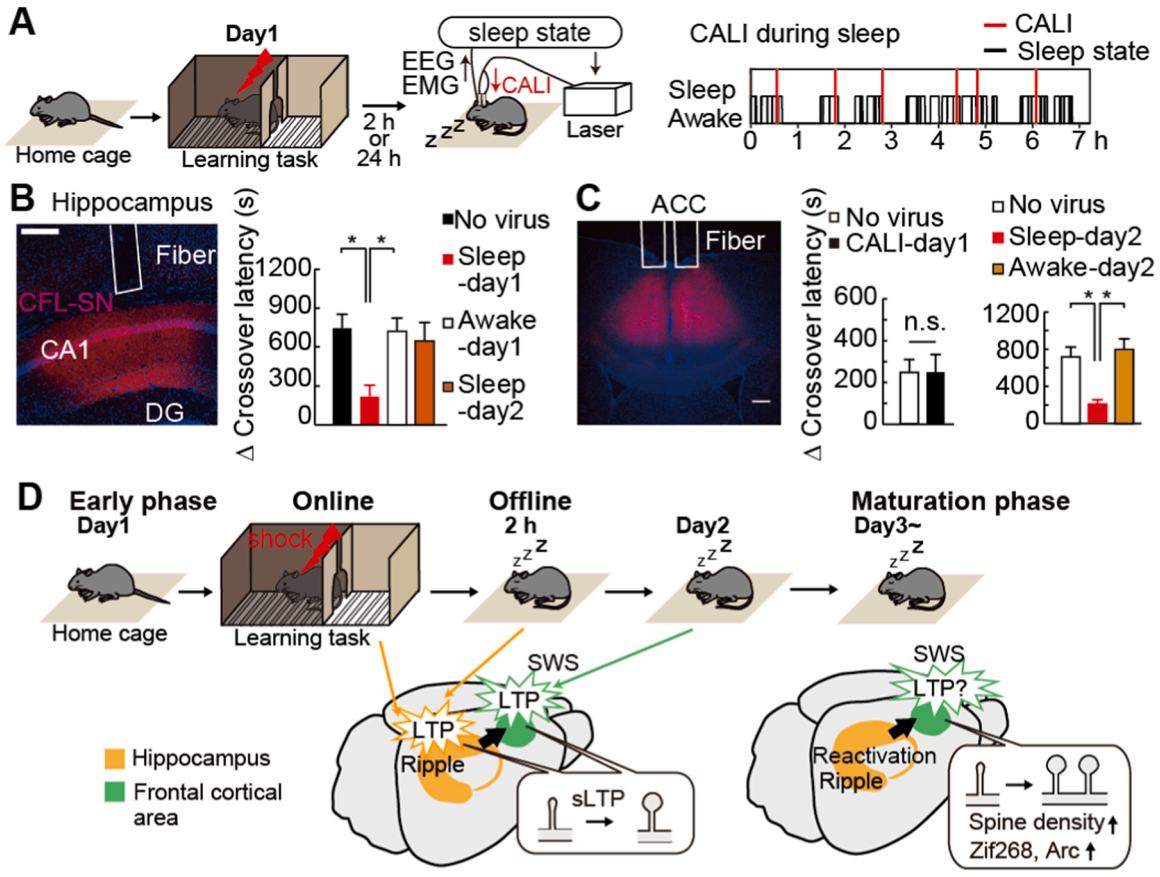

Fig. 3. Offline synaptic plasticity during sleep in hippocampus and cortex during memory consolidation, (A) After the learning task, EEG and EMG were recorded in the home cage to automatically detect a behavioral state. Light was illuminated during sleep or wake periods lasting for ≥ 20 min. An example of sleep states and light illumination (red line) is shown, (B) CALI of CFL-SN in the hippocampus erases memory during sleep on the same day, but not the next day. Light was illuminated either during sleep (Sleep-day1) or wake (Awake-day1) periods commencing 2 h after shock, then crossover latency was recorded in the following day. The experimental group (Sleep-day 2) received light during sleep on the next day and were returned to the IA box on day 3. (C) Unlike the hippocampus, CALI of CFL-SN in ACC on day1 had no significant effect on memory (black bar). In contrast, light illumination either during sleep or during wake 1 day after shock erases memory, indicating offline LTP during sleep on next day in ACC is required for memory formation, (D) A possible model of post-learning hippocampal and cortical synaptic plasticity, based on the previous studies (Goto et al., 2021; Kitamura et al., 2017). Offline hippocampal LTP occurs during sleep on the same day of shock. Offline cortical LTP occurs during sleep on the following day, which is presumably induced by replay in hippocampus. In the maturation phase, coordinated activity between hippocampus and cortex during sleep, promote changes in spine density and a gradual stabilization of memory in the cortex, The figures A-C are modified from Goto et al. (2021).

strengthening their binding through Hebbian LTP mechanisms and stabilizing hippocampal memory traces. We will refer to this type of LTP as offline LTP, as opposed to online LTP that takes place during, or immediately after a memory-forming event. The concept of offline LTP is supported by a recent study using the CALI method for spatiotemporal specific cancellation of LTP as described above (Goto et al., 2021). The study expressed CFL-SN in the hippocampus and induced CALI 2–8 h after learning, when the animals are in their home cage and allowed to sleep (Fig. 3). Importantly, CALI was effective in impairing memory recall only when it was conducted during sleep, but was ineffective if carried out during wakefulness. In addition, induction of CALI more than one day after the learning did not erase memory. Thus, this study confirms the importance of LTP contributing to the offline consolidation of memories following learning, particularly during sleep. It should be noted that although this study did not directly examine whether LTP is induced by replay during non-REM periods, the results remain consistent with the two-step consolidation theory.

On the other hand, the synaptic homeostasis hypothesis predicts a global increase in synaptic transmission during wakefulness and a decrease during sleep (Tononi and Cirelli, 2014). Consistent with this model, hippocampal neurons progressively increase their firing rate during wakefulness, while showing a decrease during sleep (Grosmark et al., 2012; Miyawaki and Diba, 2016). Moreover, it has been shown that SWRs during non-REM sleep, actually trigger LTD-like suppression of synaptic transmission (Norimoto et al., 2018).

These two mechanisms, the active memory consolidation and the synaptic homeostasis, are not mutually exclusive, rather likely occurring in parallel in the brain, as suggested by the current experimental data. When some of the synaptic inputs in a neuron are potentiated by Hebbian mechanisms, neurons scale down the overall input activity to maintain a firing rate range, a mechanism called homeostatic plasticity (Turrigiano, 1999). Therefore, offline LTP during sleep may be accompanied by downscaling utilizing this homeostatic plasticity mechanism.

At this point, it is not known whether the online LTP and offline LTP occur at the same synapse or not. It is possible that offline LTP occurs in the same synapse. In this case, the role of offline LTP would be to reinforce the online LTP, which would otherwise decay over time. Alternatively, online LTP and offline LTP may take place at different synapses, thereby playing qualitatively different roles in memory. Studying this would require labeling of the synapses that underwent LTP, for example, by SynTagMA (Perez-Alvarez et al., 2020) or As-PaRac1 (Hayashi-Takagi et al., 2015), possibly in combination with *in vivo* high resolution two-photon microscopy. Additionally, it is not known whether offline synaptic plasticity occurs during REM or non-REM sleep. The time window of CFL-SN is about 20 min whereas the duration of non-REM and REM sleep in rodents is much shorter (Fulda et al., 2011). Therefore CFL-SN is not suitable for specifically erasing LTP during REM or non-REM sleep. For this purpose, an optogenetic method with a much shorter time window, such as photo-activatable AIP (PA-AIP) would be required (Murakoshi et al., 2017).

6. Cortical synaptic plasticity during sleep and memory consolidation

Similar to hippocampal offline LTP induced by reactivation of hippocampal neurons during sleep, synaptic plasticity is thought to also occur in the cortex by the hippocampal reactivation during sleep (Fig. 1B) (Frankland and Bontempi, 2005). Evidence for the necessity of cortical neuronal activity during sleep in memory consolidation has been reported. After rats explored a novel environment, *Zif268*, an immediate-early gene product, was upregulated during the subsequent sleep in the piriform and frontal cortices (Ribeiro et al., 1999). Blockade of synaptic transmission and plasticity in the orbitofrontal cortex by injecting antagonists of glutamate receptors for 12 days after the post training period (of a social transmission of food preference paradigm) impairs the remote memory, but not if the manipulation is performed between days 15–27 (Lesburgueres et al., 2011). Similarly, a pharmacological or genetic blockade of the NMDAR subunit NR2B in the anterior cingulate cortex 1 day after training, leads to impairments of contextual fear memory (Zhao et al., 2005). Finally, overexpression of myocyte enhancer factor 2 (MEF2), a transcription factor which negatively regulates spine growth, in anterior cingulate cortex (ACC) 1 day after training, blocks both spine enlargement and remote memory (Vetere et al., 2011), indicating that structural synaptic plasticity in the ACC after learning is required for memory consolidation.

Recent spatiotemporal analysis of synaptic plasticity using the CALI method identified a time window of synaptic plasticity during sleep in the ACC (Goto et al., 2021). This study showed that cancellation of LTP in the ACC during sleep one day after learning, leads to memory erasure in the subsequent day, indicating that LTP occurs in the ACC during sleep one day after learning (Fig. 3). The same manipulation 25 days after the learning was not effective. This is consistent with other studies reporting rapid cortical synaptic plasticity after learning, although most of them did not show the involvement of sleep (Vetere et al., 2011).

After learning-induced rapid formation of a memory trace by offline LTP, further maturation is required for memory consolidation (Tonegawa et al., 2018). Kitamura et al. demonstrated this by blocking the output from engram cells in the hippocampal dentate gyrus to mPFC neurons one day after training, and found increases in the density of mPFC dendritic spines during memory consolidation is dependent on offline hippocampal activity (Kitamura et al., 2017). This study suggests that following the rapid generation of a cortical memory engram after learning, there is a further hippocampal dependent maturation process through offline input reactivation, which occurs over weeks. Similarly, the artificial induction of hippocampal LTP in intact animals during awake periods, upregulates *Zif268* during subsequent sleep in multiple cortical regions (Ribeiro et al., 2002), indicating that hippocampal LTP during sleep is sufficient to promote cortical synaptic plasticity.

On the other hand, downscaling of cortical synaptic plasticity during sleep is also reported, which is consistent with the synaptic homeostasis hypothesis. An electron microscopic study revealed the axon-spine interface in mouse motor and sensory cortices globally decreased following sleep (de Vivo et al., 2017). Synaptic AMPAR levels have also been shown to be reduced after sleep, indicating functional synaptic strength is weakened during sleep (Diering et al., 2017; Vyazovskiy et al., 2008). Further evidence comes from *in vivo* time-lapse imaging studies which demonstrate a downscaling of spine morphology in motor cortex during sleep after motor learning (Miyamoto et al., 2021). Further advances in optical techniques may enable investigation of spine morphology in brain regions other than cortex during the long process of memory consolidation in the future.

7. Molecular changes in synapses associated with sleep

What is the intracellular signaling mediating these changes in synaptic structure and transmission? Studies from brain tissue samples of both awake and asleep animals found changes in both the transcriptome and synaptic proteome (Diering et al., 2017; Noya et al., 2019), with the majority of proteins showing either up or downregulation. Homer, also known as Vesl, is one such protein that is upregulated during sleep (Diering et al., 2017; Kato et al., 1998). It functions as a postsynaptic scaffolding protein, which cross links various synaptic proteins including Shank, metabotropic glutamate receptors and IP_3 receptors, forming a meshwork-like structure at the postsynaptic density (PSD) (Brakeman et al., 1997; Hayashi et al., 2009; Tu et al., 1998). There are two alternatively spliced forms of Homer, each with different regulation of expression. A long tetrameric form of Homer is constitutively expressed and works as a meshwork of PSD (Hayashi et al., 2009). In contrast, a short monomeric Homer is induced activity-dependently (Brakeman et al., 1997). This short form acts as a natural dominant negative subunit to disrupt the meshwork and shrinks the dendritic

spine (Hayashi et al., 2009; Sala et al., 2003; Zeng et al., 2018), resulting in an overall reduction in synaptic transmission. Interestingly, expression of the short form of Homer (which is regulated by noradrenaline and adenosine signaling) is increased during sleep, likely indicating a role in the homeostatic scaling of synapses (Diering et al., 2017).

In addition to the proteome, the phosphoproteome is also dynamically regulated by sleep (Bruning et al., 2019; Diering et al., 2017; Ode and Ueda, 2020; Wang et al., 2018). Studies have shown that sleep deprivation abolishes the changes in phosphoproteome, arguing that it is regulated by sleep itself, rather than *via* the circadian rhythm (Bruning et al., 2019). Among different signaling molecules, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), a kinase highly implicated in synaptic plasticity (Kim et al., 2016; Yasuda et al., in press) has been repeatedly detected in these studies, partly due to its abundance but also to its functional importance (Bruning et al., 2019; Diering et al., 2017; Tatsuki et al., 2016). Autophosphorylation of threonine (T) 286, which renders CaMKII constitutively active, is significantly decreased during sleep, whereas autophosphorylation of T310 located within the calmodulin binding regulatory domain and likely inhibits the binding, is increased, indicating an overall suppression of CaMKII activity during sleep (Diering et al., 2017). In contrast, knockout animals of CaMKII are generally hyperactive and have reduced sleep duration (Tatsuki et al., 2016; Yamasaki et al., 2008). Overall, there remains much to be learnt with regard to both the molecular background and mechanisms underlying synaptic plasticity that takes place offline during sleep.

8. Conclusive remarks

In this review, we primarily focus on the hippocampo-cortical coordination and synaptic plasticity occurring during sleep and memory consolidation. The hippocampus and SWRs act as a key coordinator between various regions, bridging the spatial gap and acting to synchronize activity across distant regions and ultimately leading to plastic changes at synapses that support the formation of stable memories. Advances in optogenetics and imaging techniques for synaptic plasticity during sleep and combining them with electrical recording of coordination among brain regions during sleep will provide a more comprehensive understanding of the role of sleep in memory consolidation. Further study of how these regions interact and how synaptic plasticity emerges during sleep will lead to a more comprehensive understanding of memory consolidation.

Competing interests

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Data availability

No data was used for the research described in the article.

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Author contribution

Jointly written by A.G. and Y.H.

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