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Diverse synaptic mechanisms underlying learning and memory consolidation

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Memory consolidation is defined as the process by which labile short-term memories are stabilized and transformed into persistent long-term memories. This process relies heavily on synaptic plasticity, particularly long-term potentiation and depression (LTP and LTD, respectively), which have been extensively investigated in previous studies. The advent of optical tools that allow the observation and manipulation of LTP and LTD *in vivo* has advanced our understanding of their roles in learning and memory consolidation. In addition to LTP and LTD, recent research has indicated the presence of a more rapid plasticity mechanism, termed behavioral timescale synaptic plasticity (BTSP), which is crucial for encoding space and context. Sharp-wave ripples and sleep also play indispensable roles in memory consolidation, with some studies alternately linking them to LTP and LTD. At the systems level, sharp-wave ripples and sleep contribute to the transmission of information to broader brain areas, as well as the modification of synaptic strength in cortical areas for the long-term storage of memory. Furthermore, recent findings have highlighted the role of non-neuronal cells in learning, as they modulate synaptic plasticity in various ways.

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Introduction

Synaptic plasticity, defined as the ability of synapses to flexibly modify their connection strength in response to activity, underpins learning and memory [1]. Donald Hebb's hypothesis, commonly summarized as "neurons that fire together, wire together," posits that repeated activation of postsynaptic neurons by presynaptic inputs enhances synaptic efficiency, forming the basis of learning and memory [2]. This hypothesis was validated by the discovery of long-term potentiation (LTP), a long-lasting increase in synaptic efficacy that persists for hours to days following high-frequency stimulation of the dentate gyrus in rabbit brains [3]. LTP is primarily driven by an increase in the volume and AMPA receptor density in postsynaptic spines, while increased neurotransmitter release at presynaptic terminals is also involved with LTP induction [4,5]. Numerous studies have indicated that LTP, which strengthens the connections between neurons that constitute the memory trace, is crucial for memory consolidation at various stages in the brain [6,7]. Conversely, synapses can be functionally suppressed through long-term depression (LTD), which involves a decrease in the AMPA receptor density at the postsynaptic spine, and sometimes a reduction in neurotransmitter release from presynaptic terminals [8]. LTD may play a vital role in memory consolidation by pruning synapses and maintaining synaptic homeostasis, particularly during sleep, to reduce the burden of irrelevant information and preserve synaptic resources, thereby allowing further learning during wakefulness [9]. LTP and LTD are essential substrates underlying synaptic plasticity, which together enable the long-term storage of memories at both the local and systems levels. Additionally, behavioral timescale synaptic plasticity (BTSP) underlies the rapid formation of hippocampal place cells, which contribute to the spatial aspects of episodic memory [10,11]. Unlike Hebbian plasticity, BTSP allows the potentiation and depression of synapses which receive the input 2−3 s before and after neural firing thereby enabling place cell formation after a brief exploration of a novel environment [12,13]. Furthermore, non-neuronal cells such as astrocytes, microglia, and pericytes play critical roles in synaptic plasticity and memory formation, contributing to synapse formation, neurotransmitter release, and pruning of unnecessary spines. In this review, we examined the results of recent studies that offer novel insights into the role of synaptic plasticity, particularly focusing on contemporary topics, including tools for observing and manipulating synaptic plasticity, synaptic plasticity during sleep, and the associated roles of glial cells.

Induction of synaptic plasticity upon learning

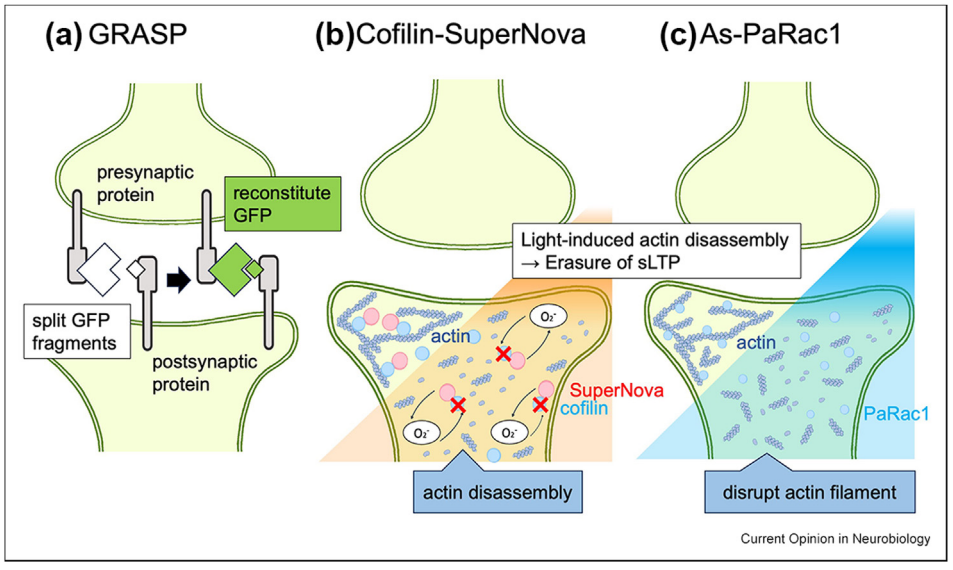
Novel optical tools for the observation and manipulation of LTP

To investigate the relationship between LTP and learning, various optical tools for synaptic visualization and manipulation have been developed in recent years. Some of these tools leverage key features of LTP, such as the increased postsynaptic spine volume/density. Green fluorescent protein reconstitution across synaptic partners (GRASP) is a method for visualizing synapses involving the reconstitution of GFP fragments expressed on presynaptic and postsynaptic membranes into functional GFP [14] (Fig. 1A). A modified GRASP method was used to visualize increased synapse numbers between the CA3 and CA1 engram neurons, which are believed to form memory traces [15–17] following contextual fear conditioning (CFC) [5]. Similarly, neurotransmitter release from engram presynaptic (CA3) neurons and AMPA receptor numbers in engram postsynaptic (CA1) neurons are enhanced [5]. Currently, GRASP is used for *in vivo* imaging to track synaptic engrams over time [18]. Structural LTP (sLTP), characterized by postsynaptic dendritic enlargement, also occurs when LTP is induced. sLTP-induced spine enlargement can increase glutamate release by applying mechanical pressure to the presynaptic terminals [14]. Direct evidence of the necessity of sLTP for learning stems from optogenetic tools used to specifically cancel it [19]. One such method, chromophore-assisted light inactivation (CALI), disrupts the function of the target molecules through light illumination. SuperNova, a photosensitizer protein used in CALI, releases reactive oxygen, thereby inactivating the fused molecule after illumination at a specific wavelength [20] (Fig. 1B). Disruption of cofilin, an actin-binding protein crucial for spine enlargement, via CALI in the CA1 region immediately following an inhibitory avoidance (IA) task impaired contextual fear memory formation [21]. These findings indicate that sLTP occurs in the hippocampus immediately after learning and is required for memory formation. Similarly, the synaptic optoprobe AS-PaRac1 (activated synapse targeting photoactivatable Rac1) labels spines in a potentiation-specific manner, and its photoactivation induces shrinkage of the labeled spines [22] (Fig. 1C). Optical shrinkage in the primary motor cortex reverses recently acquired motor learning, indicating that motor learning is acquired through synaptic potentiation [22].

BTSP: a new form of synaptic plasticity

Intriguingly, some forms of learning cannot be explained using the Hebbian plasticity rule. The hippocampus, which is critical for episodic memory formation, contains abundant place cells that are believed to constitute the cognitive map of the brain and create spatial memory [10,11]. Although LTP and LTD have been reported to underlie the stability of place cells [23,24], their rapid induction cannot be fully explained by conventional plasticity. Recent studies have proposed that rapid place cell formation in novel environments is achieved through behavioral timescale synaptic plasticity

Figure 1



Novel optical tools for the observation and manipulation of LTP. **a.** GRASP (Green fluorescent protein reconstitution across synaptic partners): Fragments of split GFP expressed on pre- and post-synaptic membranes are reconstituted to form GFP upon synapse formation. **b.** Cofilin-SuperNova: Light-induced production of reactive oxygen species (O2-) by SuperNova disrupts cofilin function, leading to actin disassembly and cancellation of the sLTP. **c.** AS-PaRac1 (activated synapse targeting photoactivatable Rac1): Photo activation of PaRac1 induces the disassembly of polymerized actin, which leads to the shrinkage of the potentiated synapses.

(BTSP), non-Hebbian plasticity [12,13]. In this paradigm, a hundreds-of-milliseconds long dendritic plateau potential initially emerges when mice are running near the future place field; synapses that receive inputs a few seconds before and after this plateau potential are significantly potentiated (or depressed) to form a new place field of place cells [12,13,25]. This is essentially different from the conventional spike-timing-dependent plasticity (STDP) in the extended time scale because STDP allows the potentiation of presynaptic input only when the postsynaptic neuron spikes within a tens-of-milliseconds window. The extended time scale for synaptic potentiation of BTSP allows for the flexible coding of places based on context [26]. Input from CA2/3 is required for place field formation via BTSP in CA1, while input from the entorhinal cortex layer III modulates the synaptic weight to reflect the presence of rewards in the CA1 spatial representation and its optogenetic inhibition results in the reduction of the probability of the plateau potential generation [12,25,27,28]. However, the mechanisms in which plateau potential is precisely generated in dendrites *in vivo* remain unclear. BTSP traits in the CA1 were also observed through studies using large-scale calcium imaging with GCaMP under natural conditions [29]. BTSP is believed to be primarily mediated by postsynaptic depolarization involving NMDA receptors, voltage-dependent calcium channels, αCaMKII phosphorylation, and calcium release from the endoplasmic reticulum to the CA1 apical dendrites [13,30,31]. However, the precise mechanisms underlying BTSP and its role in more complex learning-related representations is to be investigated. As optical voltage imaging advances, recording the membrane potentials of multiple neurons at subcellular resolution *in vivo* [27] may help clarify these mechanisms.

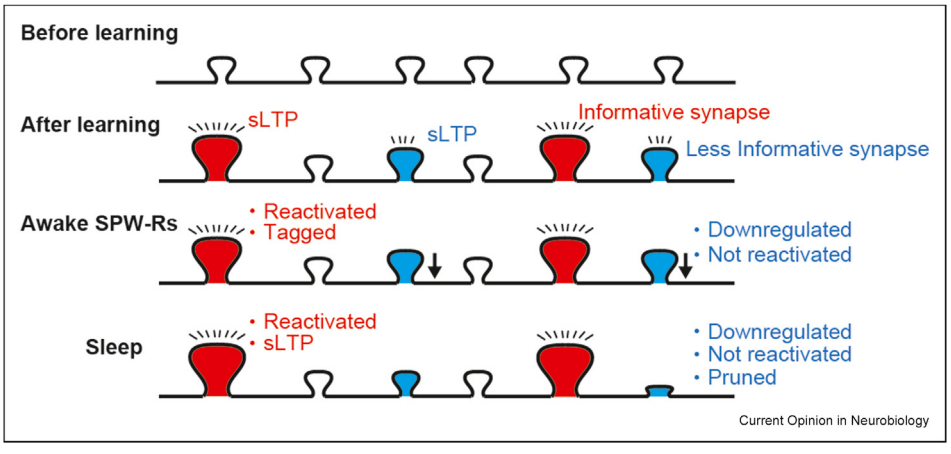
Synaptic plasticity during the offline consolidation

Offline synaptic plasticity in local circuits

Once certain synapses are strengthened by learning, they can either be maintained for long-term storage or downscaled to erase unnecessary information and conserve resources for further learning during subsequent wakefulness. Sharp-wave ripple (SPW-R), which frequently occurs in the CA1 during post-learning wakefulness and non-REM sleep, is essential for offline consolidation (after subjects experience the event) [32], as suppressing and extending SPW-Rs following a spatial memory task impairs and enhances memory retention, respectively [33,34]. Neural ensembles active during an experience are activated during SPW-Rs (i.e., reactivation), preserving the temporal order of the experience in a time-compressed manner (i.e., replay) [32]. During SPW-Rs, the CA1's overall synaptic strength is downregulated, but synapses in engram neurons and place cells encoding a novel environment are more resistant [35]. This suggests that "informative synapses" selectively survive the downregulation of synapses during SPW-Rs. In support of this, informative input to CA1, such as that relevant to reward presence, is selectively reactivated during SPW-Rs [36]. The information selected for reactivation during awake SPW-Rs is further consolidated during sleep [37] (Fig. 2).

SPW-Rs are abundant during sleep, and many studies have found that sleep is crucial for memory consolidation [38], and the relationship between memory consolidation and reactivation/replay in SPW-Rs during sleep has been extensively investigated. Sleep deprivation deteriorates SPW-R quality, impairing the reactivation and replay of experiences during the prior awake

Figure 2



Scheme of synaptic plasticity during offline consolidation: sLTP occurs in both informative and less-informative synapses after learning. During awake SPW-Rs, informative synapses are selectively reactivated and tagged for further consolidation during subsequent sleep. In contrast, less-informative synapses are not reactivated and are downregulated. When mice are asleep, informative synapses are reactivated and further potentiated, while less-informative synapses remain non-reactivated, downregulated, and may even be pruned.

period that cannot be rescued by subsequent sleep recovery [39]. This indicates a unique role of memory consolidation during sleep. Further validating the importance of sleep in memory consolidation, sleep deprivation leads to decreased spine density and dendritic spine length in the CA1, with the inhibition of the cAMP phosphodiesterase PDE4A5 rescuing these effects, restoring object-recognition memory [40]. The significance of cAMP upregulation in memory consolidation has also been reported in Ref. [41]. These findings, along with those of several additional studies [42–44], indicate that cAMP signaling pathways are strongly involved in the consolidation of hippocampus-dependent memories. Notably, the cAMP pathway facilitates memory consolidation by inactivating downstream cofilin activity [40,42,44], whereas cofilin inactivation prevents sLTP formation [21], and its overexpression enhances short- but not long-term memory independent of AMPA receptor trafficking [43]. Therefore, cofilin may play a distinct role in memory acquisition and consolidation. Notably, our recent study, which showed that optogenetic cancellation of sLTP in CA1 during sleep impaired fear memory formation, demonstrated the importance of sLTP in memory consolidation during sleep [21] (Fig. 2).

Although LTP that occurs during sleep is crucial for memory consolidation, the overall neural activity and synaptic strength in the brain gradually decrease during sleep [9]. For example, young adult-born neurons in the dentate gyrus (DG-ABNs), which are essential for hippocampus-dependent memory generation despite representing only a small population [45], show decreased activity during REM sleep compared with the wakefulness and non-REM phases. However, their downregulation during REM sleep is necessary for enhancing synaptic strength in the DG-ABNs and memory formation [46]. Future studies are needed to address the precise mechanisms by which the decreased activity of DG-ABNs during REM sleep influences local and brain-wide synaptic connections and neural activity. In the motor cortex, spines are pruned during REM sleep, which is crucial for the retention of acquired motor learning and the long-term stabilization of unpruned spines [47]. From the perspective of synaptic homeostasis, this downregulation may be beneficial for the maturation of important synapses. Despite differences in memory type, this supports the idea that important synapses survive, whereas less important synapses disappear (Fig. 2). As discussed above, the importance of the downregulation of synaptic strength and neural activity during sleep and SPW-Rs for memory consolidation has been underscored in recent studies. However, evidence showing the direct contribution of specific types of plasticity mechanisms (e.g., LTD) to memory consolidation is limited. Tools that can inhibit LTD with high temporal, spatial, and cell type specificity, such as PhotonSABER [48], will be powerful tools for addressing this question in the future.

Offline synaptic plasticity in brain-wide regions

We reviewed the plasticity involved in the offline consolidation process, primarily focusing on the hippocampus. However, in rodents, episodic memory is transferred to widespread cortical regions over weeks or months for long-term storage after temporary storage in the hippocampus for days or weeks [6]. Synaptic plasticity underlies this process, termed systems memory consolidation. The medial prefrontal cortex (mPFC) is one of the most extensively studied sites for remote episodic memory storage. Engram neurons, labeled by the early immediate gene *c-fos*, become rapidly apparent in the mPFC after a fear experience [49,50] but are not naturally reactivated by recent memory recall, although artificial reactivation successfully induces recall of the recent fearful memory in mice [50]. This study reported that spine density significantly increased on day 12 compared to day 2. Additionally, another study demonstrated that synaptic connections in local mPFC circuits and mPFC-basolateral amygdala (BLA) projections were strengthened on day 28 compared to day 7 [51]. These findings strongly indicate that gradual increases in synaptic density and the strengthening of synaptic connections in these circuits may facilitate the functional maturation of mPFC engrams. Increased expression of genes related to neurotransmitter release and dendritic spine organization at remote time points is likely to underlie this synaptic enhancement [52]. Previous studies have reported that dorsal CA1-retrosplenial cortex (RSC)-mPFC synaptic projections induce the maturation of mPFC engram assemblies [53]; however, direct synaptic connections from the dCA1 to the mPFC [53,54], as well as the dCA1-anteromidial thalamus-mPFC pathway [55], may play overlapping roles in remote memory formation. Notably, hippocampal SPW-Rs activate regions brain-wide [56–59] and mPFC synapses are preferentially activated during SPW-Rs by the firing of place cells rather than non-place cells in the CA1 [60], indicating the selective transfer of memory-related information from the hippocampus to the mPFC via SPW-Rs.

Although synaptic plasticity undoubtedly underlies the maturation of remote memories, it remains unclear when synaptic strengthening in the mPFC occurs. Some studies have indicated that the induction of synaptic plasticity as synaptic remodeling in the mPFC begins immediately following learning, accompanied by the upregulation of immediate early genes and other plasticity-related markers soon after the CFC [61,62]. Moreover, optogenetic suppression of the anterior cingulate cortex (ACC), a subregion of the mPFC, disrupts the plasticity induction in the entorhinal cortex-hippocampus system [61]. This disruption is reflected

in the lack of freezing behavior at both recent and remote time points [61]. Additionally, given that monosynaptic input from the ACC to the hippocampus provides top-down regulation to drive memory recall one day following acquisition, it is possible that changes in mPFC synapses begin by this time point [63,64]. Our study demonstrates that sLTP in the ACC plays a critical role in memory consolidation, not immediately after learning but beginning from sleep on day 2 [21].

Non-neuronal regulation of synaptic plasticity

Studies on neurons have dominated the synaptic plasticity research; however, recent studies have highlighted the significant role of non-neuronal cells in regulating synaptic plasticity. Interestingly, astrocytes in the CA1 stabilize LTP for long-term maintenance through intracellular mRNA translation and secretion of molecules into neurons [65,66]. These factors contribute to the formation of engram cells in the mPFC by facilitating *c-fos* expression in mPFC neurons that receive monosynaptic inputs from dCA1 engram neurons [54,67]. In addition, astrocytes are reportedly involved in synaptic potentiation and pruning, possibly contributing to the maintenance of synaptic homeostasis, which is needed for proper learning and memory formation [68,69]. Furthermore, microglia accelerate dendritic spine formation by engulfing the extracellular matrix [70] and actively pruning non-active synapses [71], both of which might be beneficial for effective formation of important memories. Pericytes, a type of cell that surrounds capillaries and small blood vessels, represent another non-neuronal cell type that modulates synaptic plasticity. Insulin-like growth factor 2 (IGF2) is secreted from pericytes in response to neural activity and is necessary for long-term memory formation; its overexpression induces stronger memory [72]. IGF2 stabilizes early LTP by binding to the IGF2 receptors (IGF2R) abundantly expressed in neurons [73,74]. However, the mechanism by which the IGF2R pathway modulates synaptic function remains largely unknown. Given that the binding of ligands to the IGF2R triggers protein degradation [75], future studies may need to investigate how IGF2R endocytosis triggers protein degradation through autophagy and the subsequent increase in translation [76], considering that autophagy modulates both pre- and post-synaptic plasticity and upregulates post-learning translation [77–80].

Conclusion

In this study, we reviewed the recent findings on the synaptic foundations of learning and memory consolidation. Overall, various plasticity mechanisms play interconnected roles in learning and memory consolidation over multiple timescales. The active roles of non-neuronal cells, particularly astrocytes, microglia, and pericytes, in the regulation of synaptic plasticity have been elucidated. Methods to selectively impair specific types of plasticity (e.g., CALI, AS-PaRac1, and PhotonSABER) *in vivo* have provided direct evidence of the synaptic mechanisms underlying learning and memory consolidation. Notably, CALI demonstrated that sLTP is indispensable for memory formation during its acquisition and the subsequent sleep. While the down-regulation of neural activity during sleep is likely to be crucial for healthy memory consolidation and other cognitive functions, direct evidence on how and for what purpose synaptic weight and neural activity are down-scaled during sleep remains lacking. Future studies should address this question by utilizing tools to selectively impair LTD or other forms of synaptic depression, and/or through electrophysiological recordings or spine-resolution optical imaging during sleep. We propose that synapses active at specific locations or during learning-related events (referred to as "informative synapses") are preferentially reactivated and exhibit resistance to synaptic down-regulation during subsequent sharp-wave ripples. An important avenue for future research is to determine whether and how informative synapses are selectively potentiated, while other synapses (i.e., "less-informative synapses") are down-regulated or pruned over the course of memory consolidation. Additionally, elucidating the role of these synapses in successful memory recall remains a critical question to address. Notably, future *in vivo* voltage imaging techniques should allow chronic recording of changes in membrane potential from many neurons to facilitate our understanding of how synaptic plasticity governs memory consolidation and behavior at multiple timescales.

Author contributions

Conceptualization: Y.M. and A.G. Funding acquisition: Y.M. and A.G. Writing the original draft: Y.M. Writing the review and editing: A.G.

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Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

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

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** of outstanding interest

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