

The memory orchestra: the role of astrocytes and oligodendrocytes in parallel to neurons

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For decades, the study of memory has been neuron-centric, yet neurons do not function in isolation. Today we know that neuronal activity is modulated by the environment within which it occurs, and is subject to modulation by different types of glial cells. In this review we summarize recent findings on the functional roles of astrocytes and oligodendrocytes, two major types of glia cells in the adult brain, in memory formation and its cellular underpinnings across multiple time points. We will discuss the different methods that are being used to investigate the astrocytic and oligodendroglial involvement in memory. We shall focus on chemogenetics and optogenetics, which support genetically specificity and high spatiotemporal resolution, attributes that are particularly well suited to the investigation of the contribution of unique cell types at the different stages of memory formation.

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Introduction

Memories are first acquired through different sensory modalities and encoded in various brain networks (e.g. hippocampus, amygdala) as fragile internal representations, which gradually stabilize through a process termed consolidation. This process occurs on different time scales following the acquisition stage: recent memory involves relatively fast processes, taking place during the first hours following learning on the synaptic level (synaptic consolidation). Remote memories, on the other hand, are consolidated over much longer time periods in a process termed ‘systems consolidation’, involving the interaction between multiple brain regions to enable the persistence of the memory [1].

Learning and memory rely on the coordinated neuronal activity within and between different brain regions. The activity level of neurons and the inter-regional communication are contingent on the environment within which they happen, regulated by glia cells like astrocytes and oligodendrocytes. Indeed, pioneering studies have shown that astrocytes monitor and directly modulate neuronal activity in the ‘tripartite synapse’, in which they do not merely encapsulate and insulate synapses, but also sense and actively modify synaptic transmission and plasticity [2–4]. Oligodendrocytes (OLs), responsible for wrapping axons in myelin sheaths in the CNS, were considered until recently to only insulate electrical axonal activity. However, recent evidence demonstrates that they are continuously generated in the adult brain from oligodendrocytes precursor cells (OPCs) [5–7], and this new myelination can create new sheaths, change sheath thickness and tune axonal conduction velocity, affecting spike-time arrival and synchronization in neuronal activity. Moreover, recent studies demonstrated that myelination shapes the function of neuronal circuits in an experience-dependent manner. Preventing adult myelination, either through conditional deletion of the transcription factor *myrf* or via epigenetic blockade of OLs differentiation, impaired motor skill learning and function a few weeks after manipulation [6,8]. On the contrary, inducing OPC proliferation in the premotor cortex via optogenetic stimulation of cortical layer V projection neurons, increased the amount of newly generated oligodendrocytes and myelin sheath thickness in the stimulated premotor circuit and also enhanced motor performance [6]. Taken together, these data motivate the study of astrocytes and OLs in memory as they suggest they both modulate neuronal activity through various memory-related mechanisms, such as synaptic plasticity and temporal coincidence of neuronal activity.

To study the role of astrocytes and OLs at different memory stages, we need to manipulate them within specific brain regions in a time-restricted manner. Many studies have examined the role of glia in memory (reviewed in Refs. [9,10]), employing either pharmacology (e.g. Ref. [11]), which can be reversible but not cell-type specific, or genetic manipulations (e.g. Ref. [12]) that target specific cell types but lack temporal and spatial precision. Chemogenetic and optogenetic tools are optimal for studying glial involvement in memory, as they allow reversible cell-type specific manipulation, as well as temporal and spatial precision [13]. For example, a commonly used chemogenetic approach employs engineered

human muscarinic G-protein coupled receptors (GPCRs) which respond only to the designer drug Clozapine-N-Oxide (CNO) and termed Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) [14]. As it relies on the administration of a drug to activate the designer receptors, the temporal resolution of this technique is on the order of minutes to hours, making it less suitable for precise manipulations, but nonetheless advantageous when examining memory stages that are days apart. Optogenetics rely on light-sensitive proteins (opsins), which can be ion channels, ion pumps, or GPCRs, that are activated by a specific light wavelength [15]. As light delivery is controlled on a millisecond timescale, the length of activation depends on the dynamics of the opsin, ranging from milliseconds to minutes. Recently, these tools have been successfully integrated into the research of astrocytes, and have already advanced our understanding of how memories are formed. For OLs, such tools are missing and thus the study of their involvement in memory is limited. Still, recent innovative studies employed advanced techniques to gain time-dependent genetic control over OPCs or OLs, shedding light on the functional involvement of these cells in learning and memory. In this review we will focus on recent studies investigating the involvement of astrocytes and oligodendrocytes in orchestrating the spatiotemporal coordination of neuronal activity at the different stages of memory, from acquisition, through recent memory retrieval to remote recall.

Glia in short-term memory

Short-term memory (STM) is the ability to retain newly acquired information for short durations. The immediacy of STM demands rapid synaptic alterations and does not involve prolonged protein synthesis processes. Recent studies on glial involvement in STM shed light on its underpinnings.

Astrocytic effects on short-term memory

To investigate the direct astrocytic involvement in the acquisition of short-term memories, one must manipulate astrocytes during acquisition, and shortly after examine memory. Three recent studies employed chemogenetic and optogenetic tools to activate the Gq-pathway in CA1 astrocytes and found that this manipulation can enhance short-term memory [16*,17*,18*]. Specifically, astrocytic activation with the Gq-DREADD hM3Dq improved the recognition of a novel arm in the T-maze test 5 min after the initial exposure, which took place 30 min after CNO injection [16*]. Gq-coupled opsin melanopsin mediated activation in CA1 astrocytes during training also enhanced novel object discrimination 30 min later [17*], demonstrating astrocytic activation-mediated STM enhancement. Astrocytes were also shown to affect working memory, the ability to retain and manipulate information for short durations. Specifically, photostimulation of melanopsin-expressing astrocytes in the medial prefrontal

cortex (mPFC) resulted in an increased discrimination index in the object in place (OIP) preference test [18*]. Consistently, Pinto-Duarte *et al.* showed that transgenic mice that completely lack the inositol 1,4,5-trisphosphate receptor type 2 (Ip3r2^{-/-} mice) suffered from chronic disruption of astrocytic calcium signaling and exhibited reduced performance in the Y-maze compared to wild-type mice [19*]. In addition, genetic ablation of GABA_B receptors (GABA_BRs) in mPFC astrocytes impaired performance in OIP test, providing an additional implication for the involvement of astrocytes in working memory [18*]. The cortical manipulation seems to affect working memory through activation of astrocytic GABA_BRs by parvalbumin interneurons, tuning cortical gamma oscillations [18*] (Figure 1a, lower panel). Interestingly, Lee *et al.* demonstrated that transgenic mice with disrupted vesicular release in astrocytes, showed reduced cortical gamma oscillations but maintained normal performance in the a spatial working memory task (i.e. Y maze) [20]. While Mederos *et al.* and Lee *et al.* results link astrocytes with gamma oscillations, further research is needed to resolve their contribution to working memory. To conclude, these studies exemplify the importance of integrating high spatiotemporal tools in research into the role of glia in memory, as they can uncover significant functional roles for these cells even at the brief, minutes-long process of memory acquisition.

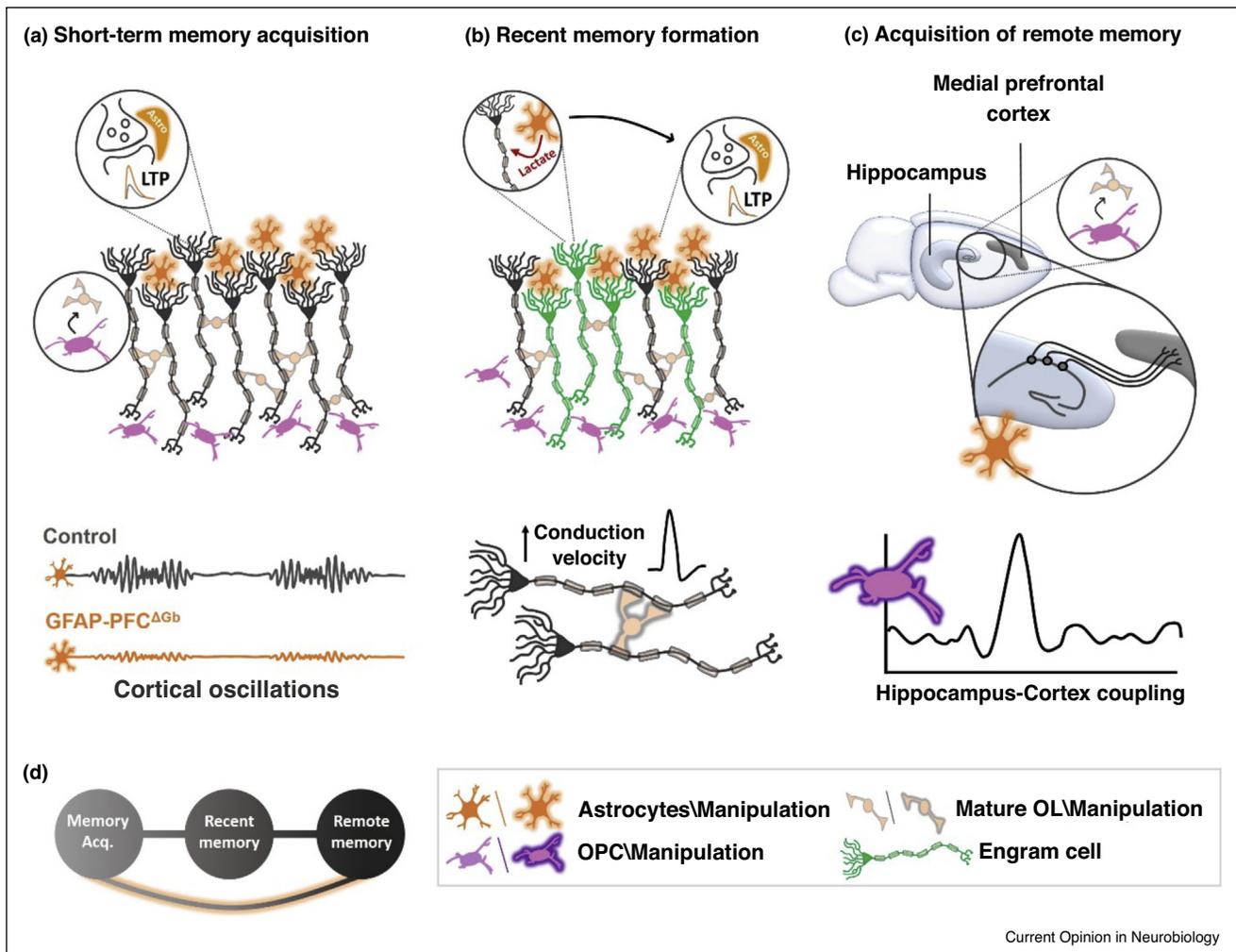
Oligodendroglial effects on short-term memory

Oligodendrocytes were thought to just insulate axons, yet surprising recent studies have shown that adult oligodendrogenesis is correlated with the level of neuronal activity [5–7]. Hence, myelination can operate together with synaptic plasticity to assimilate new information in neuronal networks, and thus be especially relevant to memory acquisition. Consistently, two recent studies have found that chronically decreasing activity-regulated myelination and myelin content, either via the conditional removal of brain-derived neurotrophic factor (BDNF)-TrkB signaling pathway on OPCs or by inhibiting neurons at the mPFC using Gi-DEADDs, impaired short-term memory formation in adjusted novel object recognition test (i.e. with a short delay between the training and the testing phase) [5,7]. Yet, the direct and specific involvement of OLs in memory acquisition is still unclear as both studies started to manipulate activity-dependent myelination long before the memory was acquired (~1 month) (Figure 1a, top panel).

Glia in recent memory consolidation

After a memory is acquired it depends on a consolidation process to become stable. Synaptic consolidation transforms information into a long-term memory via changes in gene expression and protein synthesis at the relevant synapses in the neural circuits.

Figure 1



Overview of astrocytic and oligodendroglial contribution to memory formation. **(a)** Upper panel: Chemogenetic hippocampal astrocytic activation (orange) induces LTP. Decreasing activity-dependent myelination via OPCs (purple) before acquisition impairs memory acquisition [5,7]. Lower panel: Genetic ablation of mPFC astrocytic GABA_BRs (GFAP-PFC Δ Gb) reduces the power of low gamma oscillations (30–60 Hz) during forced alteration task and impairs working memory [18]. **(b)** Upper panel: Both chemogenetic and optogenetic hippocampal astrocytic manipulation (orange) induces LTP and augments the acquisition of recent contextual memory [16*,24*]. Moreover, the same manipulation during learning enhances memory allocation (green) and short-term memory [16*,17*]. Astrocytes provide lactate to neurons which is required for LTP and recent memory formation, based on chronic astrocytic manipulation (orange) in transgenic mice before acquisition [11,28–33]. Lower panel: sustained manipulation of mature OLs (glow grey) before acquisition increases axonal conduction velocity and enhances spatial and contextual memory [40]. **(c)** Upper panel: Gi-pathway activation of CA1 astrocytes (glow orange) during acquisition disrupts CA1-ACC communication and impairs remote, but not recent, memory [25*]. Lower panel: Steadman *et al.* found that cortical inhibition of oligodendrogenesis via manipulation of OPCs (purple) immediately after training blocked hippocampal ripple-cortical spindle coupling and impaired remote memory consolidation [38*]. Pan *et al.* [41*] found that neuronal responses to conditioned context cues evolve over time in the mPFC, but not in animals that cannot form new myelin. **(d)** Scheme showing the gradual consolidation from acquisition to remote memory. The astrocytic experiment in Section (c) [25*] suggests that remote memories can stem directly from acquisition, and not only from recent memory as previously thought. Thus, a new path (marked in orange) can be added to the classic scheme from acquisition, through recent to remote memory.

Astrocytic effects on recent memory consolidation and synaptic plasticity

Astrocytic involvement in recent memory formation was examined by both loss of function, as well as gain of function experiments. Mice with impaired astrocytic exocytosis exhibited defective spatial and recognition long-term memory [21,22]. These behavioral deficits

were rescued by administration of exogenous gliotransmitters such as D-serine, immediately after memory acquisition but not one hour later, indicating early astrocytic involvement in the process of memory consolidation [21]. Interestingly, activating both chemogenetic GsPCR and optogenetic Channelrhodopsin-2 in astrocytes resulted in reduced spatial and contextual recent memory

[23,47]. On the other hand, in experiments performed in our lab, in which we expressed hM3Dq in CA1 astrocytes, we observed that CNO administration before fear conditioning resulted in increased freezing one day later, when the mice were placed back in the conditioning context, indicating improved memory of the context. These findings suggest that astrocytes confer their cognition-enhancing effects during memory acquisition, and possibly early consolidation (as CNO can remain in the body several hours after administration), but not during memory recall. To demonstrate the involvement of astrocytes specifically at the acquisition stage, we employed the optoA1 opsin in astrocytes and administered light only during the 5-min training session. Remarkably, light administration during training resulted in 90% elevation in contextual freezing in OptoA1 mice tested a day later, suggesting astrocytic involvement in recent memory acquisition [16[•]]. Astrocytic-mediated recent memory augmentation was also demonstrated by Nam *et al.*, who found that chronic pharmacological activation of CA1 astrocytic μ -opioid receptor, a Gi-coupled receptor, drives the acquisition of contextual memory associated with conditioned place preference (CPP) [24[•]]. Interestingly, acute chemogenetic activation of the Gi pathway in CA1 astrocytes via Gi-DREADDs during either fear conditioning or recall did not induce any significant effect on recent memory [25[•]]. While these studies demonstrate astrocytic involvement in recent memory formation, they also emphasize the need of future research to decipher the interplay between astrocytic-mediated memory effects (i.e. impairment and enhancement) and the different signaling pathways in astrocytes.

Learning and memory are well associated with activity-dependent synaptic alterations and astrocytes were shown to be necessary for long-term synaptic potentiation (LTP) [26,27] (Figure 1b, upper panel). Accordingly, in most of the above astrocytic-induced memory impairments and enhancements, LTP was either impaired or enhanced, respectively ([16[•],17[•]] Figure 1a upper panel, [21,24[•]] Figure 1b upper panel). Moreover, astrocytic Gq-pathway activation via Gq-DREADDs induced *de novo* NMDA-dependent LTP [16[•]], demonstrating that astrocytic activity is not only necessary but also sufficient to induce LTP.

Taken together, these studies indicate that astrocytes affect the acquisition and initial consolidation of recent memories. This effect was accompanied by astrocytic-mediated long-term changes in synaptic potentiation.

Astrocytic metabolic support of recent memory formation

Synaptic consolidation comprises sequential high-demanding energy processes, such as gene transcription, protein synthesis and post-translational modifications, that enable the stabilization of newly acquired

information. To allow intact memory consolidation, neurons need to be provided with real-time metabolic support. Several recent studies showed that astrocytes supply lactate to neurons during various learning and memory tasks, such as context avoidance [11,28,29], spontaneous alteration [30] and novel object recognition [31], via either lactate monocarboxylate transporters (MCTs) or by the use of glycogen phosphorylase inhibitor [32]. On the other hand, reducing astrocytic supply of lactate, either by knocking down hippocampal MCT1 and MCT4 [11] or by continuous long administration of β 2-adrenergic receptor agonist [31], suppresses LTP [11] and impairs memory recall [31]. Taken together, these studies suggest that astrocyte-neuron metabolic coupling is required for LTP and recent memory formation [33] (Figure 1b, upper panel).

Astrocytic effects on memory allocation

During memory allocation neuronal ensembles (also referred to as ‘engram cells’) are selected to serve as the physical basis of specific memories [34]. This selection process appears to be non-random and biased by the level of neuronal excitability. For example, when a small number of neurons are active during training, they are more likely to be allocated to the engram supporting an acquired memory [35]. Moreover, increasing the activity of a small neuronal population in the BLA before FC acquisition can improve fear memory [36,37]. Activity-dependent memory allocation raises the question of whether the previously described astrocytic-induced memory enhancement [16[•]] could stem from a tailored response of astrocytes to the activity of their surrounding neurons, that is, can astrocytes affect memory allocation? We have shown that *in vivo* hippocampal astrocytic activation via Gq-DREADDs increased neuronal activity during memory acquisition only when coupled with learning but not in home-caged mice. Moreover, the same astrocytic manipulation enhanced recent memory recall [16[•]]. Taken together, these results suggest a task-dependent enhancement of memory allocation, mediated by astrocytic activation (Figure 1b).

Oligodendrocytes affects recent memory formation

OLs were also found to affect recent memory formation, as demonstrated by Steadman *et al.* [38[•]]. In this study, the authors examined the necessity of oligodendrogenesis for the different stages of spatial memory by using transgenic mice in which OPCs were prevented from maturing into oligodendrocytes in a temporally controlled manner, starting either at acquisition or during consolidation of spatial memory. Reduced adult oligodendrogenesis in the cerebral cortex and anterior corpus callosum during the training period resulted in impaired recent spatial and contextual memory [38[•]]. Consistently, Wang *et al.* demonstrated that inhibiting adult oligodendrogenesis and myelination in the cortex can impair spatial memory [39[•]]. Both studies manipulated OPCs to

examine the effect of adult oligodendrogenesis and myelination on memory performance. Jeffries *et al.* tested the direct contribution of mature oligodendrocytes, instead of OPCs, to recent memory formation. They found that sustained activation of the extracellular signal-regulated kinases 1 and 2 in pre-existing OLs of adult mice for 5 or 10 consecutive days, before the start of the behavioral tasks, increased conduction velocity in the corpus callosum and spinal cord through expansion of myelin thickness and enhanced spatial and contextual memory [40] (Figure 1b, lower panel). To conclude, adult oligodendrogenesis and myelination are not only essential for recent memory but also capable of enhancing it.

Glia in remote memory

Systems consolidation gradually reorganizes long-term memories over distributed brain regions to store and retain remote memories. While it is known that this reorganization spans the hippocampus and frontal cortex, the exact temporal dynamics of this process is not clear. Exploring glial effects on remote memory formation may shed light on the long-term dynamics of systems consolidation.

Astrocytic effects on hippocampal-prefrontal interactions in remote memory formation

Recently, we showed, for the first time, that astrocytes can participate in the acquisition of remote memories. In this study, astrocytic Gi activation in the dorsal hippocampus during learning resulted in a specific impairment in remote, but not recent, memory recall accompanied by decreased neuronal activity in the anterior cingulate cortex (ACC) during retrieval [25^{*}]. Moreover, we revealed a massive recruitment of ACC-projecting CA1 neurons during memory acquisition, a process specifically inhibited by astrocytic manipulation (Figure 1c, upper panel). This surprising astrocytic capability to modulate inter-regional neuronal communication is also supported by previous findings demonstrating the necessity of astrocytic exocytosis for hippocampal–prefrontal synchronization [22]. So far, it was assumed that remote memory is the product of recent memory. However, this behavioral phenotype shows that the foundation of remote memory can be independently established during acquisition (Figure 1d). Astrocytes were also found to affect remote memory recall through local synaptic mechanisms. Lee *et al.* showed that impaired astrocytic exocytosis in transgenic mice decreased the power of cortical gamma oscillations, and impaired mice performance in the remote novel object recognition test [20]. Moreover, Pinto-Duarte *et al.* [19^{*}] showed that chronic disruption of calcium signaling in astrocytes did not affect recent memory recall but resulted in impairment in remote memory recall of fear, spatial and recognition memories. Yet, due to the implementation of chronic astrocyte manipulation in this study, temporal precision is not

available, and the exact timing of astrocytic involvement cannot be determined (Figure 1c).

Oligodendroglial effects on prefrontal-hippocampal interactions in remote memory consolidation

As opposed to memory acquisition and early consolidation, systems consolidation spans long periods of time and thus is temporally compatible with the weeks-long maturation process of OPCs to myelinating OLs. Indeed, it was recently demonstrated that oligodendrogenesis occurs in frontal cortical regions during spatial and contextual memory consolidation [38^{*},41^{*}], and that inhibiting it immediately after training impairs remote memory recall. Preventing the formation of new myelin before remote recall did not affect memory retrieval [38^{*}] suggesting that new oligodendrocytes are required for the acquisition and consolidation of remote memory. Furthermore, while Pan *et al.* [41^{*}] showed that neuronal responses to cues associated with the conditioned context were found to evolve over time in the mPFC, this did not occur in animals that cannot form new myelin. This cortical involvement was also demonstrated by Steadman *et al.* [38^{*}], who showed that spatial learning promotes hippocampal ripple-cortical spindle coupling which can be blocked by decreased adult oligodendrogenesis (Figure 1c, lower panel). Together, these studies show that adult oligodendrogenesis shapes the activity of neuronal circuits, which in turn affects the acquisition and consolidation of remote memories.

The study of glia in memory and the dynamics of memory consolidation

Prominent theories based on human and animal studies suggest that the consolidation of remote memories is a dynamic process which first requires hippocampal activation, and later becomes independent of the hippocampus, instead relying on frontal cortical regions [42,43]. However, this temporal separation between hippocampal and frontal cortex in recent and remote memory is not rigid: We Ref. [44] and others Refs. [45,46] have shown that the hippocampus is still critically involved in remote retrieval, and frontal areas are required for recent memory. The accumulated evidence from the study of glial involvement in memory seem to support the notion that memory representation in both the hippocampus and frontal cortex changes as the memory ages, as do the connections between them, and this co-evolution of local ensembles and inter-region connectivity mediates the selection and persistence of recent and remote memories.

Future perspectives

The studies of the role of astrocytes in memory formation vastly outnumber those focusing on oligodendrocytes (Figure 1). This imbalance might stem from technical reasons, as astrocyte research is blessed with a range of real-time spatiotemporal tools supporting their bi-directional manipulation, while OL research is relatively

impoverished in this sense. Further development of tools supporting high spatiotemporal control will elaborate the study of glial involvement in memory formation. As the molecular mechanisms underlying astrocytes or oligodendroglial involvement in memory are still being discovered, adapting existing chemogenetic and optogenetic tools to OLs and OPCs and continuing their use in astrocytes is expected continue to advance our knowledge on their involvement in memory, in a time-restricted manner.

To conclude, much like a group of musicians in an orchestra who need to be coordinated to create a harmonic symphony, activity of neuronal ensembles must be precisely synchronized to form intact memory. Astrocytes and oligodendrocytes, which were considered irrelevant to learning and memory for a long time, may assist in conducting this synchronization via their recently discovered effects on synaptic plasticity and conduction velocity. Future investigations, utilizing astrocytic calcium imaging in awake rodents during acquisition and recall, as well as electrophysiological recordings together with astrocyte or OL manipulation during learning, memory consolidation and retrieval from memory-related brain areas (such as the hippocampus and ACC) are expected to further shed light on the underlying mechanisms. Lastly, after separately describing the astrocytic and oligodendroglial dynamics during memory acquisition and recall, the real-time crosstalk between these two cell populations should be examined as it is expected to enable substantial progress in our contemporary understanding of memory formation.

Conflict of interest statement

Nothing declared.

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