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Editorial

The Emerging Role of Astrocytes in Learning and Memory Recall

Kecan Li[1,2], Yihui Cui[1,2,*]

[1]Department of Psychiatry of Sir Run Shaw Hospital and School of Brain Science and Brain Medicine, Zhejiang University School of Medicine, 310058 Hangzhou, Zhejiang, China

[2]NHC and CAMS Key Laboratory of Medical Neurobiology, MOE Frontier Science Center for Brain Science and Brain-Machine Integration, State Key Laboratory of Brain-Machine Intelligence, Zhejiang University, 310058 Hangzhou, Zhejiang, China

*Correspondence: yihuicui@zju.edu.cn (Yihui Cui)

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Astrocytes, anatomically and functionally interact with neurons within tripartite synapses, and critically regulate synaptic transmission and neural circuit dynamics. In a groundbreaking study published in Nature, Williamson *et al.* [1] identified a specialized subpopulation of hippocampal astrocytes—termed learning-associated astrocyte (LAA)—that dynamically respond to learning events and orchestrate memory encoding and retrieval processes.

Recent evidence has suggested that various brain functions are mainly executed by a small population of experience-activated neuronal ensembles within specific neural circuits (so called "engram" cells) [2,3]. As a major part of tripartite synapses, astrocytes are considered as playing key roles in regulating synaptic plasticity, as well as its associated brain functions [4]. Previous studies have demonstrated that astrocytes exhibit experience-dependent plasticity by dynamically adapting their activation states, transcriptional responses, and functional properties in response to extrinsic stimuli and intrinsic cellular conditions [5,6]. However, whether there are subsets of experience-activated astrocytes that are closely affiliated with "engram" neurons and if they form durable ensembles in responding and regulating associated brain functions remain elusive. Utilizing activity-dependent strategies, Williamson *et al.* [1] identified a causal role of a small population of learning-responsive astrocytes ensembles in hippocampal memory encoding and retrieval processes.

The fundamental question pursued by the authors was whether astrocytes function as an active component of the engram in hippocampus-dependent learning and memory processes. In this study, authors observed an activity-dependent increase in c-Fos expressing astrocytes triggered by a contextual fear-conditioning model. The c-Fos expression is triggered directly by local experience-responsive neuronal ensembles, as chemogenetic activation within local hippocampal excitatory neurons was sufficient to induce c-Fos expression in neighboring astrocytes. In addition, astrocyte-specific Fos conditional knockout diminished long-term potentiation (LTP) in hippocampal neurons and impaired performance in both contextual fear conditioning and novel place recognition tasks in mice. These data indicated that activity-dependent astrocyte activation is essential for synaptic plasticity and learning-dependent behaviors.

Intriguingly, guided by innovative activity-dependent viral strategies, Williamson *et al.* [1] successfully labelled the LAAs in an experience-dependent manner. Moreover, they recorded spontaneous Ca^{2+} activity in labelled astrocytes with two-photon imaging of acute slices and observed an elevated Ca^{2+} activity activated by fear-learning. Complex intracellular calcium signals in astrocytes reflect interactions with neurons and can influence associated circuits [7–9]. For learning and memory retrieval, ensembles of neurons and the synaptic plasticity are essential cellular bases, inspiring further investigation to examine the interactions between LAAs and hippocampal engram neurons within a single learning event. Indeed, the authors optimized the tagging system to specifically label both LAAs and engram neurons in fear-learning, revealing that the processes of engram neurons were preferentially localized in the domains of LAAs. Following engram-engram synapses labelling similarly showed that synaptic engram was enriched in the territories of LAAs, indicating the coordinated interactions between LAAs and engram neurons.

Given that LAAs are juxtaposed with engram neurons, the authors performed multi-disciplines of strategies to investigate how LAAs regulate neuronal engram activity. Chemogenetic activation of LAAs induced a robust induction of LTP in hippocampal slices, and selectively increased the frequency of excitatory postsynaptic currents (EPSCs) in engram neurons without affecting EPSC amplitude. Furthermore, in a modified fear-learning paradigm, Williamson *et al.* [1] observed that an increasing reactivation rate of fear-tagged engram neurons was induced by activation of LAAs during post-learning retrieval in mice. Notably, the increase of freezing behavior in mice caused by LAAs reactivation can be durably observed after fear conditioning, whereas the activation of pan-astrocytes in the hippocampus showed no difference in mice behavior. Taken together, these findings imply that LAAs truly modulate the learning-associated circuits and play an essential role for memory recall.

Guided by fluorescence-activated cell sorting, transcriptomic RNA sequencing and gene expression analysis, the authors revealed that LAAs molecularly featured by an upregulation of nuclear factor I-A (NFIA). Previous studies have shown that astrocytic NFIA regulates hippocampal activity and related circuit function [7]. Here, the authors found that selective deletion of NFIA in LAAs caused less freezing behavior after fear learning in mice but showed no influence on the novel place recognition task, indicating that the expression of NFIA in LAAs is essential for memory consolidation and recall. Interestingly, artificial reactivation of engram neurons rescued the impaired freezing behavior in mice with NFIA-deficiency LAAs, emphasizing the bidirectional regulation between LAAs and engram neurons.

Taken together, the study by Williamson *et al*. [1] illustrated emerging roles of astrocytes in memory consolidation and recall, expanding the notion that astrocytes exhibit experience-dependent plasticity [10]. Current findings also foster inspiring questions. For example, what is the physiological significance of only a subset of astrocytes activation during learning process? As the astrocytes consists of functionally diverse subpopulations, further studies are also needed to clarify whether and how other astrocytes indirectly engage in the modulation of memory recall. As more researches consistently verify the transcriptional plasticity in astrocytes [7,11], future studies are needed to relate these transcriptional responses to the biochemical quanta that astrocytes use as memory substrates. Disentangling these open questions will deepen our understanding of astrocytes in learning and memory recall.

Author Contributions

YC: Writing and Supervision. KL: Original draft. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Yihui Cui is serving as one of the Editorial Board members of this journal. We declare that Yihui Cui had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

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