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Current Opinion in Neurobiology

Optimizing memory performance and emotional states: multi-level enhancement of adult hippocampal neurogenesis

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Adult hippocampal neurogenesis (AHN) plays a key role in modulating memory and emotion processing. A fundamental question remains on how to effectively modulate AHN to improve hippocampal function. Here, we review recent work on how distinct aspects of hippocampal neurogenesis, including the number, maturation state, and activity of adult-born neurons (ABNs), contribute to overall hippocampal function. We propose multi-level enhancement of hippocampal neurogenesis with the combination of increased number, elevated activity, and enhanced maturation of ABNs as a potential strategy to optimize overall hippocampal performance. In addition, integration of ABNs induces significant remodeling of the local hippocampal circuits, which may in turn modulates brain-wide network dynamics. We discuss recent progress on how integration of ABNs contributes to local hippocampal circuit and brain-wide network dynamics during behavior.

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Current Opinion in Neurobiology 2023, **79**:102693

This review comes from a themed issue on **Neurobiology of Learning and Plasticity 2023**

Edited by **Muming Poo** and **Thomas John McHugh**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.conb.2023.102693

Introduction

The adult mammalian hippocampus contains quiescent neural stem cells in the dentate gyrus (DG) that upon activation generate new neurons throughout life. These adult-born neurons (ABNs) undergo a critical period of heightened activity and synaptic plasticity from 4 to 8 weeks after birth, during which hippocampal circuits undergo significant remodeling [1–6]. Ample studies using rodent models have established the causal role of ABNs in regulating memory performance and emotional states, two key functions of the adult hippocampus [7,8]. In addition, dysfunction of ABNs has been shown to causally contribute to the cognitive and affective deficits associated with various brain disorders [9,10].

Although still under debate, the existence of adult neurogenesis in the human hippocampus has gained increasing support from recent evidence using fate markers such as thymidine analog and carbon dating [11–13], immunohistology of neurogenesis markers with improved protocols in human tissues with shorter postmortem times [14,15], and single-nucleus RNA sequencing from postmortem tissues [11,16]. It is generally agreed that low-level hippocampal neurogenesis exists in adult humans across aging potentially via low-frequency de novo generation and protracted maturation of ABNs [11]. A fundamental question remains on how to effectively modulate low-level neurogenesis to improve hippocampal function.

Here, we review recent work on how distinct aspects of hippocampal neurogenesis, including the number, maturation state, and activity of ABNs, contribute to overall hippocampal function. We propose multi-level modulation of hippocampal neurogenesis by increasing the proliferation of neural precursors, enhancing the developmental properties critical for maturation and integration of ABNs, and promoting the activity of ABNs as a potential strategy to improve memory performance and emotional states. In addition, integration of ABNs induces significant remodeling of the local hippocampal circuits, which could in turn modulate brain-wide network dynamics. We discuss recent progress on how integration of ABNs may contribute to local and brain-wide network dynamics. The role of adult hippocampal neurogenesis has been implicated in both health and disease. Owing to the focused nature of this review, we will limit our discussion to recent studies

performed in healthy animals with the goal of applying these learned principles to various diseased conditions.

Distinct contribution of the number, activity, and maturation of adult-born neurons in hippocampus-dependent memory and emotion processing

Adult hippocampal neurogenesis (AHN) is a multi-stage process, starting from activation and fate decisions of neural stem cells, followed by proliferation and differentiation of neural progenitors, and finally maturation and integration of ABNs into the existing circuitry. AHN is dynamically regulated by various external stimuli, and ABN activity alters in response to running [17], novel/enriched environment [18], and antidepressant ketamine treatment [19]. Therefore, the number, maturation state, and activity of ABNs may collectively contribute to overall hippocampal function. Here, we review recent publications using different approaches to manipulate distinct aspects of ABNs, with the goal of dissecting the relative contribution of the number, activity, and maturation state of ABNs to distinct aspects of hippocampal function.

Number of ABNs

Early studies aiming to address the causal role of adult neurogenesis in hippocampus-dependent behaviors have mainly manipulated the number of ABNs. Decreasing hippocampal neurogenesis is often achieved by genetic ablation of neural stem/progenitor cells or focal irradiation of proliferating cells. These studies collectively suggest that ABNs are required for context discrimination [20,21], stress resilience [22,23], anti-depressant effects [24], post-training induced forgetting [25], social memory recognition [26], and preference for future awards [27]. By contrast, increasing hippocampal neurogenesis is often achieved by genetic perturbation of genes critical for the proliferation of neural progenitors or survival of ABNs. For instance, increasing the number of ABNs by deletion of pro-apoptotic gene Bax in neural stem/progenitor cells promotes contextual discrimination, a form of learning that requires an animal to distinguish between similar contexts, without altering single-trial contextual memory performance that requires an animal to distinguish between two markedly different contexts [28,29]. In addition, other major hippocampus-dependent behaviors are not affected by increased neurogenesis, including spatial memory and anxiety/depressive-like behaviors at the baseline condition [28,30]. Interestingly, increasing neurogenesis is sufficient to reduce anxiety/depressive-like behaviors in animals with chronic treatment of corticosterone [30], suggesting a role of increased neurogenesis in adaptive stress responsivity. In another example, increasing neurogenesis by overexpression of Cdk4/cyclinD1 to expand the pool of neural stem/progenitor cells improves the precision, but not the pace, in the acquisition of spatial learning [31]. These results indicate that increasing the number of ABNs mediates context discrimination, spatial precision, and adaptive stress responsivity without affecting spatial/contextual memory encoding/retravel and baseline anxiety/depression-related behaviors.

Activity of ABNs

With the advancement of circuit-based tools, increasing studies have been performed by selective manipulation of ABN activity using optogenetics or chemogenetics during behavior. Specifically, optogenetic inhibition of ABNs impairs spatial memory [5], context and location discrimination [4,32,33], and memory consolidation [34]. Chemogenetic inhibition of ABNs impairs spatial/contextual memory retrieval [18] and remote memory retrieval-induced reconsolidation [35], increases susceptibility to social defeat stress [23], and abolishes the antidepressant effects of fluoxetine or ketamine [19,36]. These studies collectively suggest that the activity of ABNs is required for memory and emotion processing.

Comparing to ABN activity silencing, increasing the activity of ABNs generates variable and conflicting results. Specifically, acute chemogenetic activation of ABNs results in improved spatial/contextual memory [18], reduced anxiety-like behavior [18,36], and antidepressive effects similar to those induced by fast-acting antidepressant ketamine [19]. By contrast, acute optogenetic activation of ABNs leads to impaired contextual memory encoding/retrieval [4] and consolidation [34]. The discrepancy in memory performance upon chemogenetic versus optogenetic stimulation of ABNs could be explained by the differences in activity patterns of ABNs induced by these two approaches. The optogenetic stimulation frequency for ABNs used in those studies is 10 Hz [4] or 20 Hz [34], which is much higher than the average firing rate of ABNs at 2.3 Hz [32]. Therefore, overstimulation of ABNs may disrupt ABN-mediated sparse coding in the hippocampus, thus leading to impaired memory. Although the firing frequency of ABNs upon chemogenetic stimulation remains to be determined, it is possible that chemogenetic stimulation of ABNs may better simulate the natural firing pattern of ABNs. Alternatively, chemogenetic stimulation of ABNs may induce the release of secretory factors unique to ABNs, such as neurotrophic factors, thus leading to improved learning and memory.

Maturation state of ABNs

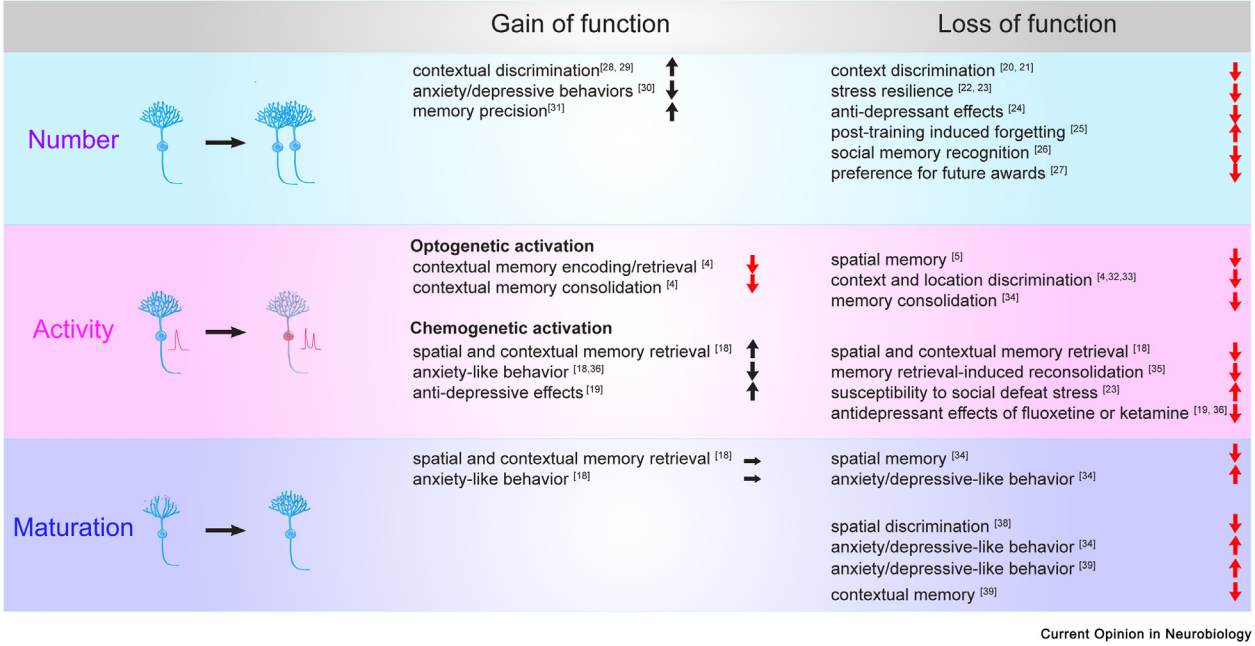
Ample studies using rodent models have established the stage-dependent role of ABNs in regulating hippocampus-dependent behaviors [4,5,32,33], thus suggesting that proper maturation of ABNs is critical for hippocampal function. Accumulating evidence suggests that dysregulation of ABN maturation leads to impaired

hippocampus-dependent behaviors. For instance, retroviral knockdown of Disrupted-in-Schizophrenia 1 leads to accelerated maturation (without altering the number) of ABNs along with impaired spatial memory and increased anxiety/depressive-like behavior [37]. Similarly, retroviral deletion of kainate receptors leads to accelerated maturation (without altering the number) of ABNs along with impaired spatial (but not contextual) discrimination [38]. By contrast, retroviral deletion of atypical Rho GTPase Rnd2 leads to delayed maturation and decreased survival of ABNs along with increased anxiety-like behavior [39]. In another study, tamoxifen-induced deletion of a voltage-gated potassium channel $K_v1.1$ in neural stem/progenitor cells leads to delayed maturation and reduced production of ABNs along with impaired contextual memory [40]. These studies collectively suggest that proper maturation of ABNs is required for maintaining the normal hippocampal function, as either accelerated or delayed ABN maturation impairs behaviors.

This raises the question of whether promoting healthy maturation of ABNs during the critical window is sufficient to improve behaviors. Our recent study has shown that enhancing the maturation along with increasing the number of ABNs by stimulating the supramammillary nucleus (SuM) in healthy young mice does not improve spatial/contextual memory performance and anxiety-like behaviors [18]. However, acute chemogenetic activation of these SuM-enhanced (as opposed to control) ABNs improves these behaviors. These results suggest that enhanced maturation along with the increased number of ABNs is required for their activity-dependent contributions to behavior. Whether enhancing the maturation of ABNs alone (without altering the number) is sufficient for these behavioral effects remains to be determined.

Taken together, these findings suggest that manipulating each individual aspect of ABNs (number, maturation, or activity) is sufficient to alter hippocampus-dependent behaviors. Importantly, distinct modes of ABN manipulation appear to impact distinct aspects of hippocampal function (Figure 1). For example, increasing the number of ABNs modulates memory discrimination (similar contexts), spatial precision, and adaptive stress responsivity, but does not affect spatial or contextual memory processing of different contexts and baseline anxiety/depression-related behaviors. However, enhancing the activity of ABNs can modulate these behavioral aspects unaffected by the increased number of ABNs, despite above-mentioned discrepancies in memory performance from optogenetic versus chemogenetic activation of ABNs. Based on these

Figure 1



Contribution of the number, activity, or maturation of adult-born neurons in hippocampus-dependentfunction. These studies suggest that manipulating each individual aspect of ABNs (number, maturation, or activity) is sufficient to alter hippocampus-dependent behaviors. Importantly, distinct modes of ABN manipulation appear to impact distinct aspects of hippocampal function.

findings, we propose multi-level enhancement of hippocampal neurogenesis with the combination of increased number, elevated activity, and enhanced maturation of ABNs as a potential strategy to optimize overall hippocampal performance.

Adult-born neurons modulate local hippocampal circuit and brain-wide network dynamics

Adult mammalian hippocampal circuits undergo significant remodeling through the integration of ABNs. Using slice electrophysiology, two-photon calcium imaging, and in vivo electrophysiology, several studies have shown that ABNs exhibit elevated excitability and activity, enhanced plasticity, and less spatial tuning during a critical time window of 4–8 weeks after birth [1,2,4,5,32], as compared to developmentally-born granule cells (mature GCs). These unique physiological properties allow ABNs to integrate differentially in the hippocampal circuits and brain-wide networks during distinct behavioral states, as compared to their mature counterparts.

Local and brain-wide inputs to ABNs

Rabies-virus-based monosynaptic retrograde tracing identifies the presynaptic inputs of ABNs during maturation [41,42]. Specifically, ABNs first receive local inputs from mossy cells and various types of interneurons (INs), such as parvalbumin (PV), and somatostatin (SST) INs, followed by brain-wide subcortical, entorhinal cortical, and intrahippocampal inputs. Interestingly, the afferent inputs of ABNs can be modified by experience, in that an enriched environment increases both intrahippocampal inputs from CA3/CA1 INs and distal inputs from the entorhinal cortex (EC), medial septum/diagonal band of Broca (MSDB), and SuM [43]. In addition, enhanced integration of ABNs leads to a scaled increase of local hippocampal inputs from mossy cells and hilar INs [44]. These findings highlight the structural plasticity of ABN afferents in response to integration state and external stimuli.

Ex vivo studies using slice electrophysiology further characterize the functional inputs to ABNs with recent studies mainly focusing on IN-ABN and EC-ABN connections. Recent studies report that PV-INs and SST-INs establish functional synapses onto ABNs at early development [45,46], but these connections require several weeks to reach functional maturation, thus enabling a mechanism for long-lasting remodeling of local circuits onto ABNs during maturation. In addition, ABNs with high intrinsic excitability exhibit low synaptic connectivity with EC [47]. Such low EC-ABN connectivity can potentially prevent ABNs from responding broadly to cortical activity [43]. These studies suggest that high IN-ABN connectivity [46] and low EC-ABN connectivity [47] collectively allow excitable ABNs to contribute to sparse coding.

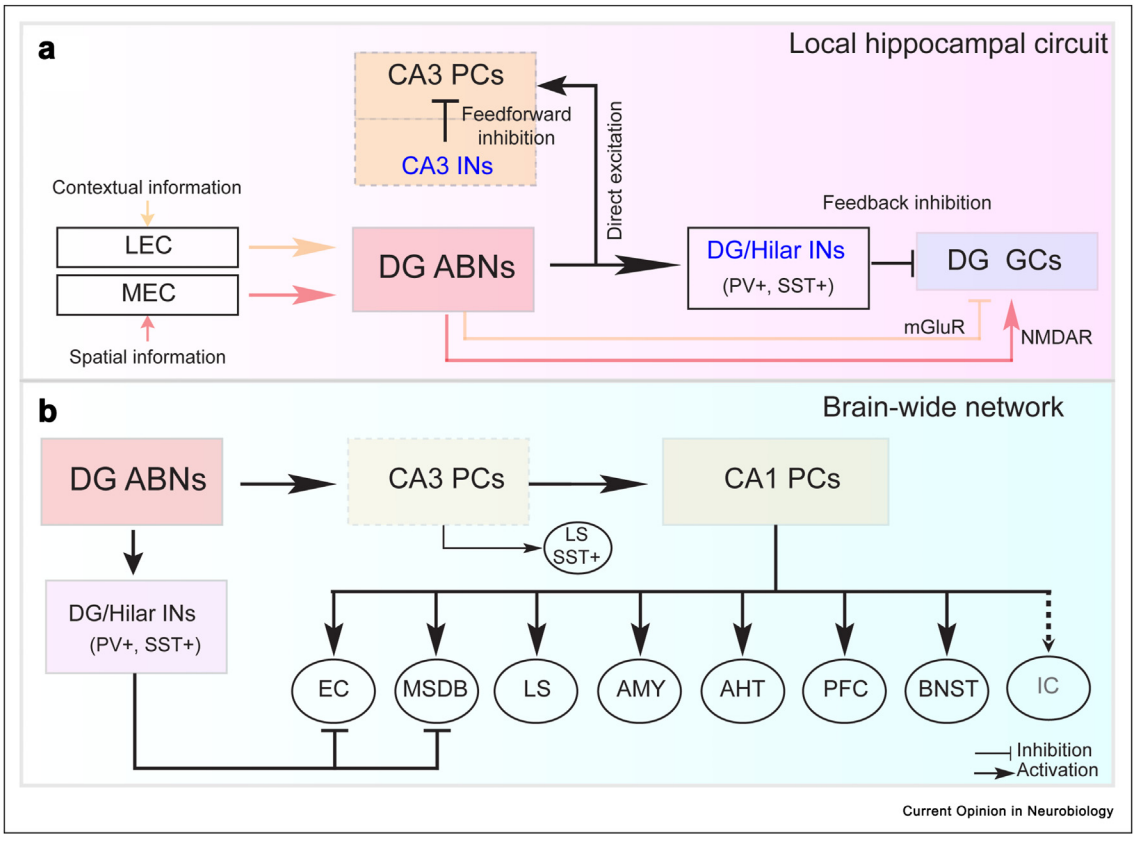
Modulation of local hippocampal circuit dynamics by ABNs

In contrast to presynaptic inputs of ABNs, the outputs of ABNs are less studied. Converging evidence suggests ABNs make direct synaptic contacts through mossy fibers onto DG/hilar/CA3 interneurons and CA3 pyramidal cells (PCs) [6,48–50]. So far, most studies addressing the contribution of ABNs to the outputs of local circuit dynamics have used optogenetic manipulation. Using genetic or retroviral approaches to selectively label ABNs with channelrhodopsin, several studies have characterized how ABNs form connections with these excitatory and inhibitory neurons as they integrate into the hippocampal circuits (Figure 2a). These studies generally agree that ABNs start to form synaptic connections with DG/hilar interneurons, including PV and SST interneurons, to provide feedback inhibition onto DG mature GCs [6,46,50]. In the meanwhile, they also form synaptic connections with CA3 interneurons and PCs to provide both feedforward inhibition and direct excitation onto PCs [5]. Due to the simultaneous presence of ABN-mediated inhibition and excitation, it raises a question on the net contribution of ABNs to the activity of distinct hippocampal subfields. A recent study reports that selective activation of ABNs increases the sparsity of hippocampal population activity while suppressing ABN activity reduces this sparsity along with increased firing rates of principle cells and impaired novel object recognition [32]. These results suggest that activity of ABNs plays a critical role in maintaining the sparsity of hippocampal activity for effective mnemonic information processing.

Whether ABNs form direct connections with GCs remains elusive. A recent study reports that ABNs can form monosynaptic glutamatergic connections with DG GCs [51]. However, whether these glutamatergic connections between ABNs and GCs are excitatory or inhibitory is dependent on the inputs received by ABNs. Specifically, in response to inputs from the lateral entorhinal cortex critical for contextual information processing, ABNs inhibit mature GCs through metabotropic glutamate receptors; while in response to inputs from the medial entorhinal cortex critical for spatial information processing, ABNs excite mature GCs through ionotropic NMDA receptors [51]. These findings suggest that ABNs can directly modulate GC activity without going through local interneurons (Figure 2a).

Besides manipulating ABN activity, the hippocampal circuit dynamics have also been studied with manipulation of the ABN number. Genetic ablation of hippocampal neurogenesis increases the amplitude of gamma bursts in the DG [52], suggesting that ABNs play a critical role in regulating local interneurons that modulate mature GC activity. This idea is supported by a study in which increasing or decreasing the number of ABNs impacts the spread of activity and strength of

Figure 2



Adult-born neurons modulate local hippocampal circuits and brain-wide network. (**a**) ABNs modulate local hippocampal circuits. ABNs form synaptic connections with DG/hilar INs, including PV and SST INs, to provide feedback inhibition onto DG mature GCs. In the meanwhile, they also form synaptic connections with CA3 INs and PCs to provide both feedforward inhibition and direct excitation onto PCs. ABNs can also make direct synaptic connectionswith GCs through distinct glutamate receptors depending on the types of EC inputs. (**b**) ABNs modulate brain-wide network. ABNs can exert indirect impact on the global brain network through recruiting local INs or CA3/CA1 PCs. DG: dentate gyrus, LS: lateral septum, LEC: lateral entorhinal cortex, MEC: medial entorhinal cortex, EC: entorhinal cortex, MSDB: medial septum/diagonal band of Broca, AHT: anterior hypothalamus, AMY: amygdala, PFC: prefrontal cortex, BNST: bed nucleus of the stria terminalis, IC: insular cortex, ABNs: adult-born neurons, GCs: granule cells, IN: interneurons, PCs: pyramidal cells, PV: parvalbumin, SST: somatostatin.

neuronal activation in DG potentially through modulating ABN-mediated excitatory drive onto local interneurons [53]. In addition, selective increase of neurogenesis reduces excitatory postsynaptic currents (EPSCs) and spine density in mature neurons, whereas genetic ablation of neurogenesis increases EPSCs in mature neurons [54]. These results suggest that the number of ABNs modifies synaptic transmission to mature GCs potentially through redistribution of pre-existing synapses to newly integrated ABNs.

Modulation of brain-wide network dynamics by ABNs

One way that ABNs can potentially impact brain-wide network dynamics is through recruiting DG/hilar/CA3 cells that send long-range projections to distal brain regions (Figure 2b). Supporting this, Zhou et al. show that silencing the activity of ABNs influences the dynamics of bilateral hippocampal regions measured by functional magnetic resonance imaging (fMRI) and in vivo electrophysiology [33], potentially through contralaterally projecting hilar mossy cells or CA3 pyramidal cells. In addition, DG/hilar SST interneurons send long-range projections to MSDB and EC [55,56], and CA3 PCs directly innervate lateral septum (LS) SST interneurons [57]. Therefore, ABNs may modulate the activity dynamics of these distal brain regions through recruitment of local interneurons and CA3 PCs. Furthermore, ABNs can also modulate CA1 dynamics through ABN-CA3-CA1 connections. CA1 is broadly connected with diverse output regions [58–60], including (but not limited to) LS, anterior hypothalamus, amygdala, prefrontal cortex, and bed nucleus of the stria terminalis (Figure 2b). Therefore, modulating ABN activity may impact brain-wide network dynamics by recruiting these CA1 downstream targets. Besides direct anatomical connections between ABNs/ABN-connecting cells and their downstream targets, the hippocampus also exhibits significant functional

connectivity with brain regions that are not anatomically connected with it, such as the insular cortex [61]. Therefore, ABNs can impact brain-wide network through such functional connections. Supporting this view, we recently demonstrate that dysregulated ABNs with hyperexcitability and accelerated maturation induce aberrant activity and synchrony in CA3 and CA1 of the hippocampus, as well as distal medial-dorsal thalamus and insular cortex during a spatial memory task, novel place recognition [62]. These results suggest that ABN activity and maturation state can impact brain-wide network dynamics across several anatomically discrete regions to modulate spatial memory.

Conclusion

In recent years, there have been growing interests in the role of AHN in cognitive and emotional behaviors, as well as its contribution to local hippocampal circuit and brain-wide network dynamics during these distinct behavioral states. This article reviews a series of recent studies using different approaches to manipulate distinct aspects of ABNs and suggests that distinct modes of ABN manipulation appear to impact distinct aspects of hippocampal function. Therefore, we propose multi-level enhancement of AHN with the combination of increased number, elevated activity, and enhanced maturation of ABNs as a potential strategy to optimize overall hippocampal performance. However, a number of questions remain. First, it remains unknown how chemogenetic manipulation of ABNs contributes to local hippocampal and brain-wide network dynamics. Given the divergent behavioral effects induced by chemogenetic versus optogenetic manipulation of ABNs, it is possible that chemogenetic manipulation of ABNs exerts differential circuit effects than optogenetic manipulation of ABNs. Second, ABNs contribute to both cognitive and emotional behaviors that have been thought to be related to the functions of the dorsal and ventral hippocampus, respectively. However, it remains unknown how dorsal versus ventral ABNs contribute to local circuit and brain-wide circuit dynamics. Since dorsal and ventral hippocampus exhibit distinct output targets [58], it is possible that dorsal versus ventral ABNs may differentially modulate local circuit and brain-wide network dynamics. Third, our recent study suggests that multi-level enhancement of AHN allows a small population of ABNs to make significant contribution to hippocampus-dependent behaviors [18]. However, the local circuit and global network mechanisms underlying such behavioral modulation remain to be determined. Fourth, impaired AHN has been reported in multiple pathological conditions in humans, such as epilepsy [12], neurodegenerative diseases [11,14,15], and major depression [63]. Whether multi-level enhancement of ABNs can be applied to these conditions to achieve functional restoration remains to be determined. Together, future studies addressing these open questions will enrich our understanding of the contribution and therapeutic potential of ABNs in health and disease by modulating AHN process.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

Acknowledgments

This work was supported by grants awarded to J. Song from NIH (R01MH111773, R01MH122692, RF1AG058160, R01NS104530). Y-D. Li was partially supported by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (29600).

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