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Review

Requirement of adult-born neurons for hippocampus-dependent learning

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ABSTRACT

A fundamental question in the field of adult neurogenesis relies in addressing whether neurons generated in the adult dentate gyrus are needed for hippocampal function. Increasing evidence is accumulating in support of the notion that hippocampus-dependent behaviors activate new neurons and that those neurons are highly relevant for information processing. More specifically, immature new neurons under development that have unique functional characteristics begin to emerge as a highly relevant population in the dentate gyrus network. This review focuses on how hippocampus-dependent behaviors activate adult-born neurons and how modulation and ablation of adult hippocampal neurogenesis alter spatial and associative memory. While several contradictory findings emerge when analyzing the literature, evidence in favor of a relevant role of adult-born neurons in hippocampal function is compelling.

Contents

The dentate gyrus (DG) of the adult hippocampus is one of the two regions of the brain, together with the olfactory bulb, that produce large numbers of new neurons in mammals including humans [1]. The hippocampus has been associated with mainly two functions, the formation of memory [2] and the representation of space [3]. What is the importance of adult neurogenesis to hippocampal function? Two strategies have been primarily used to address this question: (1) to study the effect of modulation or ablation of adult neurogenesis on specific behaviors; (2) to study how particular behaviors activate adult-born neurons. In this review we focus on these two strategies and discuss important aspects related to the dynamics of the maturation of adult-born neurons and its relation to behavior.

1. Functional properties of developing DGCs are critical to their role in hippocampal function

The time required for maturation and functional integration of adult-born dentate granule cells (DGCs) is a critical determinant of their role in information processing. Newborn DGCs develop for several weeks to establish their functional properties, afferents and output connectivity [4–10]. That time is not fixed but depends on the species, since neuronal maturation occurs at a faster pace in rats than in mice [11]. In addition, the activity of the network surrounding newly generated DGCs could also influence their maturation. Different regions along the septotemporal axis of the hippocampus show different levels of activity and expression of immediate early genes (IEGs) [12]. Since local network activity can modulate neuronal maturation, the differential activation of the hippocampal network generates restricted domains where adult-born neurons mature at different rates [13].

By the end of this developmental process newborn DGCs become similar to those DGCs generated during perinatal development [14,15]. However, while developing, newborn cells display

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high input resistance, increased intrinsic excitability, and reduced GABAergic inhibition, physiological characteristics that are typical of immature neurons and make them functionally unique [4,6,16–18]. In mice, DGCs between 3 and 5 weeks of age produce action potentials in response to afferent stimulation [19], present higher levels of LTP [7] and are already connected with their postsynaptic targets [8]. The higher excitability and plasticity of immature DGCs opens the possibility that such neuronal population is mostly active in response to different stimuli in a less specific manner than mature DGCs.

2. Modulation of adult neurogenesis

The amount of neurogenesis in the DG can be importantly modulated by different factors that increase or decrease the number of newly generated DGCs that become incorporated in the circuit. It is now known that physical exercise or enriched environment increase DG neurogenesis [20–22], which is also the case for certain pathological conditions like ischemia [23] (see Table 1). On the other hand stress, aging and depression can decrease neurogenesis [24]. Some of the evidence on the role of adult neurogenesis in memory arises from experiments in which neurogenesis was increased by running and then the effects of that manipulation on learning performance were evaluated [21,25,26]. For example, running was initially shown to enhance spatial learning [21] and, more recently, it was found to exert an effect on DG-mediated pattern separation [25]. Moreover, exposing animals to an enriched environment increased neurogenesis and rendered an enhanced performance in spatial memory tests such as the Morris water maze (MWM) [27–30], in associative memory tests like instrumental conditioning [31] and also in novel object recognition tasks [32]. Interestingly, mutant mice lacking Toll-like receptor 3 (TLR3) exhibited increased neurogenesis and enhanced performance in the MWM, novel object recognition and contextual fear-conditioning tasks [33], highlighting again the relationship between DG neurogenesis and hippocampus-dependent memory performance.

Direct evidence that behavioral effects of exercise or enrichment are mediated by neurogenesis is scarce. Most studies discussed above establish a correlation between improved learning capabilities and exercise or enriched environment, conditions that are known to increase neurogenesis, but the requirement of neurogenesis is often not addressed. Enhanced learning may be due to increased neurogenesis, but it may also obey to factors other than neuronal production. As an example of the first case, enhanced novel object recognition after enrichment was abolished by antimitotic agents that block neurogenesis [32]. In contrast, other works have provided convincing evidence of improved hippocampus-dependent learning and behavior by enriched environment in the absence of neurogenesis [31,34].

Recent work has provided interesting insights about animals subjected to chronic social defeat stress. Even though it is known that stress reduces neurogenesis [35], some animals, the ones that displayed a persistent effect of stress reflected as social avoidance, exhibited increased neurogenesis presumably as a compensatory mechanism (perhaps "remembering" the stress). When neurogenesis was reduced by irradiation mice failed to display stress-induced avoidance [36]. This later experiment highlights the importance of the dynamics in the process under study. In particular the same stimulus, stress, can both decrease or increase neurogenesis and thus control behavioral output.

3. Ablation of adult neurogenesis

The most compelling evidence relating DG neurogenesis to learning and memory arises from ablation experiments. The question to be asked is: are there any alterations in learning and memory performance in animals lacking adult-born DGCs? Gathering consistent data on this fundamental question has been difficult due to the many variables involved. Those variables include animal species and strain, age of the ablated neurons, method of ablation, behavioral task and performance analysis. Thus, comparing behavioral studies from different laboratories is a complex task since there are no two studies in which most variables are the same. In mice, adult-born neurons require 3–5 weeks before they become functionally relevant to the hippocampal network (i.e. they respond to synaptic inputs, generate spikes and make synapses onto postsynaptic targets) [4,8,14,19]. This interval seems to be shorter in rats [11]. Therefore, the time between neurogenesis ablation and behavioral training defines the neuronal population that will be removed and to design meaningful experiments it should outlast the timing required for neuronal maturation. This has not always been the case [37–39]. In addition, three very different methods have been primarily used to abolish adult neurogenesis: irradiation, antimitotic agents and, more recently, inducible genetic ablations. Below we discuss the notion that the ablation method may greatly influence the outcome of behavioral experiments.

Spatial learning in the MWM and the Barnes maze, and associative learning such as contextual fear conditioning are the most commonly used tasks to assess the relevance of adult-born neurons in information processing in animals with ablated neurogenesis. Adult neurogenesis has also been involved in anxiety-related behaviors (recently revised by [40]). Analyzing spatial performance involves the ability to learn the task (acquisition period), remembering the task (short-term memory) and remembering after long delays (long-term memory). Analyzing all published data on ablation of adult neurogenesis in spatial learning shows that acquisition is impaired in some studies [41–44,46,47] whereas it is unaffected in others [39,45,48–52] (see Table 1) or even increased [53]. Interestingly, most studies do support an effect of abolished neurogenesis in either short- or long-term spatial memory [41,42,46,48,49,52], although some studies still show no effect [45,50,51].

The conflicting data on spatial learning cannot be accounted for by differences in species/strain. However, evidence seems to become more consistent when the ablation method is taken into account. Most experiments in which removal of adult neurogenesis was achieved by genetic manipulation (inducible transgenic animals or lentiviral transgene delivery) display impairment in spatial memory [41,42,44,46,48,49] (but also see [50,54]). The consistency of the inducible genetic approach might be due to the higher selectivity of the ablation, reduced degree of unspecific brain damage, and more appropriate control conditions (such as non-induced transgenic mice) compared to those of chemical antimitotic agents or irradiation.

Refining the protocols to evaluate qualitative aspects of spatial learning performance can also aid in dissecting the role of adult neurogenesis in hippocampal spatial processing. Detailed behavioral analysis in animals with ablated neurogenesis revealed impairment in learning strategies reflected as the inability to relocate a new position of a hidden platform when a previous position has been learned [43]. In addition, an impairment was observed in the ability to distinguish similar but not distinct spatial locations highlighting the role of adult neurogenesis in spatial discrimination [55].

The impact of adult neurogenesis has also been evaluated in associative memory tasks that depend on the hippocampus. Most experiments evaluating the effects of abolishing neurogenesis show substantial impairment in contextual fear conditioning. In this case, regardless on the method of choice, deficiencies are observed in both short-term [11,38,42,44,48,50,56–60] and long-term retention [56,60] (Table 1). However, there are some cases

Table 1
This table summarizes studies in three areas: modulation of adult neurogenesis and its effects on behavior, ablation of neurogenesis and its effects on behavior and activation of adult born neurons by behavior.

Method of modulation	Species	Behavior	Effect	Timing of task	Reference
Enriched environment (EE)	3-months-old Sprague-Dawley Rats	MWM	Increased performance at learning	4-8 weeks in EE or isolated environments	[28]
Enriched environment and MAM	Adult Sprague-Dawley Rats	Novel object recognition	Increased memory at 24 and 48 h and abolished by MAM	17 days from treatment	[32]
Enriched environment and irradiation	10-week-old female 129Sv/Ev mice	Novelty suppressed feeding protocol MWM	Reduced latency to feed, but not abolished by irradiation Increased performance at learning and short-term memory but not abolished by irradiation	2 months after irradiation and 6 weeks in EE	[34]
Enriched environment	3 to11-week-old male C57Bl/6 mice	MWM Acoustic startle reflex/Prepulse inhibition Passive avoidance	Increased performance in learning and short-term memory Higher inhibition No effect	8 weeks in EE	[30]
Enriched environment	3-months-old male C57Bl/6 mice	Rotarod Classical eyeblink conditioning CA3 to CA1 LTP Instrumental conditioning	Increased performance No effect No effect Increased performance	30 days in EE but failed to increase neurogenesis	[31]
Running	3-month-old female C57Bl/6 mice	MWM LTP	Increased learning. No effect on short-term memory (4h) Increased LTP in CA1	43-49 days trained with 2 trials per day	[21]
Running and irradiation	4-month-old male Long Evans rats	Contextual fear conditioning MWM	Correlation between the amount of neurogenesis and the time freezing No effect but if presented a second time the irradiated animals were impaired at learning	5 weeks after irradiation	[26]
Running	3-month-old male C57Bl/6 mice	Spatial discrimination test	Correlation between running, neurogenesis and better spatial pattern separation	38 days after running	[25]
Stress and irradiation	5 to 8-week-old male mice expressing Nestin-GFP	Stress induced social avoidance	Mice with persistent social avoidance after 4 weeks had increased neurogenesis and the behavior disappear with irradiation	Behavioral test 4 weeks after irradiation	[36]
Toll-3 like receptor deficient mice with increased neurogenesis	6 to 8-month-old male TLR3 -/- mice	MWM Novel object preference	Increased memory (72h) Increased	6-8 months old	[33]

Table 1 (*Continued*)

		Contextual fear conditioning Plus maze	Increased Reduced anxiety		

Ablation of Neurogenesis and its effects on behavior

Method of ablation	Species	Behavior	Effect	Age of New neurons	Reference
Irradiation	2-month-old male Wistar rats	Place recognition in T maze Object recognition MWM	Impaired in 8 and 21 days post irradiation No effect No effect	8, 21, 42 days after irradiation 7 and 21 days after irradiation 14 days after irradiation	[39]
Irradiation	2-month-old male C57Bl/6 mice	MWM Barnes maze	No effect on learning or short-term memory (1 h) Impaired spatial version	3 months after irradiation	[45]
Irradiation	40-day-old male Long Evans rats	MWM	No effect on the acquisition and long-term memory (1 week) Impaired longer term memory (2 and 4 weeks)	4 weeks after irradiation	[52]
Irradiation	4-month-old male Long Evans rats	Non matching to sample task (NMTS) Delayed NMST Contextual fear conditioning	No effect Impaired when intervals between sample and test trials were long Impaired short-term memory (24 h) and long-term memory (28 days)	4 weeks after irradiation	[60]
Irradiation and electroconvulsive seizure to restore neurogenesis	175-200 g male Sprague-Dawley rats	Contextual fear conditioning	Impaired short-term memory (24 and 48 h) and restored by ECS	6 weeks after irradiation or ECS, and 4 weeks after ECS	[59]
Irradiation	250 g male Long Evans rats	T maze Contextual fear conditioning	No effect Impaired short-term memory (2, 24 and 48 h)	9 weeks after irradiation	[56]
Irradiation and MAM	7 to 10-week-old male C57Bl/6 mice	Contextual fear conditioning	No effect with MAM Impaired short-term memory (24 h) only in animals with severe irradiation	3 months after irradiation or 17 days after MAM treatment	[38]
Irradiation	8 to 9-week-old male Sprague-Dawley rats	Contextual fear conditioning	Impaired short-term memory (24 h) in rats irradiated 4 or 8 weeks	3, 4, 8 weeks after irradiation	[11]

	8 to 9-week-old male C57Bl/6 mice		No effect in mice		
Irradiation or lentiviral infection with dominant negative Wnt to reduce neurogenesis	8-week-old female C57Bl/6 mice	Delayed non matching to place (DNMP) radial arm maze task	Impaired when presented at low separation in space but not at high. Impairment in spatial pattern separation	2 months after irradiation	[55]
Irradiation or follistatin over expressing transgenic mice with impaired neurogenesis	20-week-old Wistar rats 5-week-old maleC57Bl/6 mice or 20-week-old mutant mice	*In vivo* LTP Contextual fear conditioning	Prolonged in irradiated mice to 2-3 weeks No effect on short (24 h) or long-term memory (28 days). Impaired the transfer of memory from hippocampus to other areas	11 days after irradiation 5 weeks after irradiation or 20 weeks old mutant mice	[57]
MAM	Rats	Trace conditioning (hippocampus-dependent)	Impaired	14 days with MAM and test 2 days after	[47]
MAM	220 g male Sprague-Dawley rats	MWM Trace fear conditioning Contextual fear conditioning Plus maze	No effect on learning or short-term memory (24 h) Impaired No effect on short-term memory (24h) No effect	14 days with MAM and test 2 days after	[51]
DNA-alkylating agent temozolomide (TMZ)	6 to 8-week-old female C57Bl/6 mice	MWM Reversed platform in MWM	Different learning strategy Impairment in cognitive flexibility to find the platform when moved to a new position.	4 weeks after treatment	[43]
MAM	9-week-old male C57Bl/6 mice	MWM Object location test Novel object recognition	No effect on learning, impaired short-term (24 h) and long-term memory (1 month) Impaired short-term memory (24h) No effect	15 days at training and recent testing 45 days at remote testing	[37]
Irradiation and inducible transgenic strategy to ablate new neurons	>12-week-old male 129/SvEv mice >12-week-old male GFAP-Tk transgenic mice	MWM Delayed matching to place task Plus maze Contextual fear conditioning	No effect on learning No effect No effect Impaired short-term memory (48 h)	3 months after irradiation Or 6 weeks after inducing neurogenesis ablation with GCV	[50]
Irradiation and inducible transgenic strategy to ablate new neurons	>12-week-old male 129/SvEv mice >12-week-old male GFAP-Tk transgenic mice	Radial maze	Improvement of working memory when repetitive information is presented in a single day	3 months after irradiation Or 10 weeks after inducing neurogenesis ablation with GCV	[53]
Inducible transgenic strategy	2-month-old male C57Bl/6	Habituation to a novel enviroment	No effect	6-7 weeks of treatment	[41]

Table 1 (*Continued*)

to ablate new neurons	mice and Nestin-rtTA/Tet-BAX bigenic mice	MWM Contextual fear conditioning	Impaired learning and short-term memory (24 h) No effect on short-term memory (24 h)	with DOX to reduce neurogenesis	
Inducible transgenic strategy to ablate new neurons	Nestin-DTA induced with tamoxifen in C57Bl/6 background	Barnes maze spatial memory test Contextual fear conditioning	Impaired learning and long-term memory (1 week) Impaired short-term memory (24 h)	41-54 days after 4 days of tamoxifen treatment	[44]
Inducible transgenic strategy to ablate new neurons	Tlx mutant mice induced with tamoxifen	Contextual fear conditioning MWM	No effect on short-term memory (24 h and 48 h) Impaired learning and short-term memory (12h). No effect on long-term memory (3 weeks)	4 weeks after treatment	[46]
Genetic manipulation to affect the timing of differentiation of adult born neurons	3-month-old Bitransgenic Nestin-trTA/TRE-PC3 mice	MWM Radial maze Contextual fear conditioning	Impaired learning, reversal learning and short-term memory (24 h) Impaired working memory Impaired short-term memory (24 h)	After 65 of Dox induction	[42]
Inducible transgenic strategy to ablate new neurons	Nestin-tk transgenic mice and administration of GCV ablates only de dividing tk-expressing cells	MWM Contextual fear conditioning	No effect on learning or short-term memory (4 h). Impaired long-term memory (1 week) No impairment in short (24 h) or long-term (4 weeks) memory. Impaired inhibition learning in extinction	3 weeks after beginning of treatment	[48]
Lentiviral infection with dominant negative WNT	8-week-old male Sprague Dawley rats	MWM	No effect on learning. Impaired long-term memory (2-8 weeks) only in animals with severe neurogenesis ablation	8-9 weeks after viral injection	[49]
Cyclin D2 knockout mice with ablated neurogenesis	Adult Cyclin D2 knockout mice	MWM Contextual Fear conditioning Trace fear conditioning Novel object recognition	No effect on learning or memory No effect on learning or memory (36 days after) No effect or a slight improve in learning No effect	From birth	[54]
Inducible transgenic strategy to ablate new neurons	2-month-old male C57Bl/6 mice and Nestin-rtTA/Tet-BAX bigenic mice	Contextual fear conditioning in two contexts to discriminate	Impaired the ability to disambiguate two contexts during extensive training	9 weeks of treatment	[58]
Inducible transgenic strategy to increase neurogenesis using nestin-mediated ablation of BAX	Transgenic mice lacking BAX in neural stem cells when induced with tamoxifen	LTP Contextual fear conditioning Contextual fear discrimination	Increased No effect on short-term memory (24h) Higher levels of discrimination in mutant mice	8 weeks after BAX ablation	[61]

Method of stimulation	Species	Treatment	Effect in newborn neurons	Age of new neurons	Reference
Exploration in recruitment of adult born neurons	6-month-old Fisher-344 rats	Spatial exploration	The proportion of adult born neurons expressing IEG Arc was higher than the proportion in the neurons previously there	5 months old	[63]
Enriched environment in recruitment of immature adult born neurons	8-week-old C57Bl/6 mice	Exposing to EE and re-exposing 6 weeks after BrdU injection	Exposing 1-2 weeks old neurons to EE increase the number, but not the proportion, of responsive neurons to that environment when re-exposed to the same environment (using IEG cFos, Zif268 as markers of activity)	1-2 weeks at first exposure to EE 6 weeks at re-exposure	[66]
MWM in recruitment of immature adult born neurons	C57B6 male mice	Performing MWM and re-perform 10 weeks after BrdU injection	Making animals to perform MWM when neurons were between 4-6 weeks old increase the percentage of neurons responding to re-exposure to MWM (using IEG cFos and Arc as markers of activity)	4-6 weeks at first exposure to MWM 10 weeks at re-exposure	[71]
MWM in recruitment of immature adult born neurons	10-week-old male Long Evans rats	Performing MWM	MWM increased the percentage of new born neurons activated (using IEG cFos) in the ventral hippocampus	4 weeks after BrdU	[12]
MWM in recruitment of immature adult born neurons	11-week-old male C57Bl/6J	Performing MWM at day 9 and testing at day 39	The percentage of BRdU/Zif268 neurons increased when animals are exposed to re training in the same task	39 days after BrdU	[70]
MWM in recruitment of immature adult born neurons	male C57Bl/6 mice	Performing MWM and Contextual fear conditioning at different times after BrdU injection	Newborn neurons must be >5 weeks to be activated by behavior, using cFos. The rate of activation was equivalent for embryonically, postnatally or adult-generated DGCs	1, 5, 7.5 and 10 weeks after BrdU	[65]
Exploration in recruitment of adult born neurons	35 days old male Wistar rats	Spatial exploration	Increased recruitment of adult generated DGCs, using Arc. Neurons must be >30 days to be recruited.	1, 7, 15, 30, 45 days after BrdU	[64]
MWM in recruitment of immature neurons in two rat species	60-65 days old Long-Evans and Sprague-Dawley rats	Performing MWM	SD rats showed higher levels of Zif268/DCX than LE rats. LE rats had higher Zif268/16 days old BrdU in response to spatial memory.	Training 6 days after BrdU. Testing 11 days after BrdU.	[67]

Abbreviations: EE, enriched environment; MWM, Morris water maze; LTP, long term potentiation; MAM, methylazoxymethanol; Dox, doxycycline; ECS, electro convulsive shock.

where ablation of adult neurogenesis did not modify retention of contextual fear memory [41,46,48,57], but instead altered extinction of learning [48] or the transfer of that learning from the hippocampus to higher cortical areas [57]. In a recent paper, genetic ablation of adult neurogenesis did not affect the acquisition of contextual fear memory but a more complex task revealed an impaired ability to disambiguate two slightly different contexts during prolonged training [58]. In addition, mutant mice with enhanced levels of adult neurogenesis displayed improved capabilities to discriminate similar contexts [61]. Overall, experiments investigating both spatial and associative memory seem to point to an important role of adult neurogenesis for discriminating subtle differences. Thus, it becomes increasingly clearer that a more profound knowledge on DG function is necessary for understanding adult neurogenesis.

4. Activation of adult-born DGCs by behavior

In vivo activation of newborn cells after spatial learning and exploration has been primarily evidenced by using the expression of IEGs [62]. Although this is an indirect approach to measuring neuronal activity and/or plasticity, it is the most widely used method to identify active DGCs. There are two central questions that have emerged in recent years, and are central to understanding the functional role of adult neurogenesis: (1) are newborn DGCs more active than older DGCs generated during development under different behaviors? (2) Does early activation of immature DGCs determine their later recruitment? These questions are now beginning to be addressed. It is now known that adult-born neurons must be at least two to four weeks old (depending on the species) to express immediate early genes in response to behavior [63–67]. In addition, it has been shown that adult-born DGCs tend to be preferentially activated during spatial exploration when compared to the entire population of DGCs in the layer [63,64]. These findings have generated a lot of excitement because they might imply that information processing in the adult dentate gyrus is carried out primarily by adult-born neurons [68,69], which is yet to be experimentally substantiated.

It has been suggested that activation of immature neurons (few weeks old) might be important in determining their future recruitment. Neurons that were about ten days old at the time of training in the MWM were shown to be preferentially activated when animals were re-exposed to the same behavioral tasks [70], although it is unclear from this experimental approach whether the same newborn DGCs were activated during both exposures to the task. However, a similar approach using one week of exposure to an enriched environment around the second week after neuronal birth failed to show preferential activation, but did show an increase in the survival of new DGCs [66]. In addition, although preferential activation of adult-born neurons with re-exposure to the MWM has been suggested [71], more recent work from the same laboratory has provided evidence that questions this view [65]. Therefore, this critical problem in the field will demand additional work and novel tools to measure the activity of newborn DGCs in behaving animals.

5. Conclusions

Great efforts have been made to understand the contribution of new DGCs to behavior studying modulation or ablation of adult neurogenesis. While conflicting evidence in favor and against a role of adult neurogenesis in hippocampal function was found, overall there is a clear impairment in spatial and associative memory by neurogenesis ablation, especially in those studies where ablation was carried out by genetic manipulation rather than chemicals or irradiation. As knowledge on DG function and on functional properties of newborn DGCs builds up, experimental design can be refined to dissect their very specific roles. For instance, the latest studies are aiming to interrogate whether neuronal populations with unique properties such as immature DGCs impinge in spatial pattern separation. Future studies will require more powerful tools to specifically enhance or ablate adult neurogenesis in a transient and regulated manner. In addition, a more detailed behavioral analysis will be required for identifying specific tasks that depend on DG function and, in particular, on proper functional integration of adult-born neurons.

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References

[1] Gage FH. Mammalian neural stem cells. Science 2000;287:1433–8.
[2] Squire LR. The neuropsychology of human memory. Annu Rev Neurosci 1982;5:241–73.
[3] Moser EI, Kropff E, Moser M-B. Place cells, grid cells, and the brain's spatial representation system. Annu Rev Neurosci 2008;31:69–89.
[4] Esposito MS, Piatti VC, Laplagne DA, Morgenstern NA, Ferrari CC, Pitossi FJ, et al. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 2005;25:10074–86.
[5] Faulkner RL, Jang M-H, Liu X-B, Duan X, Sailor KA, Kim JY, et al. Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain. Proc Natl Acad Sci 2008;105:14157–62.
[6] Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming G-L, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 2006;439:589–93.
[7] Ge S, Yang C-H, Hsu K-S, Ming G-L, Song H. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 2007;54:559–66.
[8] Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, et al. Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 2008;11:901–7.
[9] Toni N, Teng EM, Bushong EA, Aimone JB, Zhao C, Consiglio A, et al. Synapse formation on neurons born in the adult hippocampus. Nat Neurosci 2007;10:727–34.
[10] Zhao C, Teng EM, Summers Jr RG, Ming G-L, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 2006;26:3–11.
[11] Snyder JS, Choe JS, Clifford MA, Jeurling SI, Hurley P, Brown A, et al. Adult-born hippocampal neurons are more numerous, faster maturing, and more involved in behavior in rats than in mice. J Neurosci 2009;29:14484–95.
[12] Snyder JS, Radik R, Wojtowicz JM, Cameron HA. Anatomical gradients of adult neurogenesis and activity: young neurons in the ventral dentate gyrus are activated by water maze training. Hippocampus 2009;19:360–70.
[13] Piatti VC, Davies-Sala MG, Espósito MS, Mongiat LA, Trinchero MF, Schinder AF. The timing for neuronal maturation in the adult hippocampus is modulated by local network activity. J Neurosci 2011;31:7715–28.
[14] Laplagne DA, Espósito MS, Piatti VC, Morgenstern NA, Zhao C, van Praag H, et al. Functional convergence of neurons generated in the developing and adult hippocampus. PLoS Biol 2006;4:e409.
[15] Laplagne DA, Kamienkowski JE, Espósito MS, Piatti VC, Zhao C, Gage FH, et al. Similar GABAergic inputs in dentate granule cells born during embryonic and adult neurogenesis. Eur J Neurosci 2007;25:2973–81.
[16] Couillard-Despres S, Winner B, Karl C, Lindemann G, Schmid P, Aigner R, et al. Targeted transgene expression in neuronal precursors: watching young neurons in the old brain. Eur J Neurosci 2006;24:1535–45.
[17] Snyder JS, Kee N, Wojtowicz JM. Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol 2001;85:2423–31.
[18] Wang S, Scott BW, Wojtowicz JM. Heterogenous properties of dentate granule neurons in the adult rat. J Neurobiol 2000;42:248–57.
[19] Mongiat LA, Espósito MS, Lombardi G, Schinder AF. Reliable activation of immature neurons in the adult hippocampus. PLoS One 2009;4:e5320.
[20] Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature 1997;386:493–5.
[21] van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci 1999;96:13427–31.

[22] van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci 1999;2: 266–70.
[23] Kokaia Z, Lindvall O. Neurogenesis after ischaemic brain insults. Curr Opin Neurobiol 2003;13:127–32.
[24] Duman RS. Depression: a case of neuronal life and death? Biol Psychiatry 2004;56:140–5.
[25] Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. Running enhances spatial pattern separation in mice. Proc Natl Acad Sci 2010;107:2367–72.
[26] Wojtowicz JM, Askew ML, Winocur G. The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. Eur J Neurosci 2008;27:1494–502.
[27] Dhanushkodi A, Bindu B, Raju TR, Kutty BM. Exposure to enriched environment improves spatial learning performances and enhances cell density but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats. Behav Neurosci 2007;121:491–500.
[28] Nilsson M, Perfilieva E, Johansson U, Orwar O, Eriksson PS. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. J Neurobiol 1999;39:569–78.
[29] Pham TM, Söderström S, Winblad B, Mohammed AH. Effects of environmental enrichment on cognitive function and hippocampal NGF in the non-handled rats. Behav Brain Res 1999;103:63–70.
[30] Iso H, Simoda S, Matsuyama T. Environmental change during postnatal development alters behaviour, cognitions and neurogenesis of mice. Behav Brain Res 2007;179:90–8.
[31] Madroñal N, López-Aracil C, Rangel A, del Río JA, Delgado-García JM, Gruart A. Effects of enriched physical and social environments on motor performance, associative learning, and hippocampal neurogenesis in mice. PLoS One 2010;5:e11130.
[32] Bruel-Jungerman E, Laroche S, Rampon C. New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. Eur J Neurosci 2005;21:513–21.
[33] Okun E, Griffioen K, Barak B, Roberts NJ, Castro K, Pita MA, et al. Toll-like receptor 3 inhibits memory retention and constrains adult hippocampal neurogenesis. Proc Natl Acad Sci 2010;107:15625–30.
[34] Meshi D, Drew MR, Saxe M, Ansorge MS, David D, Santarelli L, et al. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. Nat Neurosci 2006;9:729–31.
[35] Joëls M, Karst H, Krugers HJ, Lucassen PJ. Chronic stress: implications for neuronal morphology, function and neurogenesis. Front Neuroendocrinol 2007;28:72–96.
[36] Lagace DC, Donovan MH, DeCarolis NA, Farnbauch LA, Malhotra S, Berton O, et al. Adult hippocampal neurogenesis is functionally important for stress-induced social avoidance. Proc Natl Acad Sci 2010;107:4436–41.
[37] Goodman T, Trouche S, Massou I, Verret L, Zerwas M, Roullet P, et al. Young hippocampal neurons are critical for recent and remote spatial memory in adult mice. Neuroscience 2010;171:769–78.
[38] Ko H-G, Jang D-J, Son J, Kwak C, Choi J-H, Ji Y-H, et al. Effect of ablated hippocampal neurogenesis on the formation and extinction of contextual fear memory. Mol Brain 2009;2:1.
[39] Madsen TM, Kristjansen PEG, Bolwig TG, Wörtwein G. Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. Neuroscience 2003;119:635–42.
[40] Samuels BA, Hen R. Neurogenesis and affective disorders. Eur J Neurosci 2011;33:1152–9.
[41] Dupret D, Revest J-M, Koehl M, Ichas F, De Giorgi F, Costet P, et al. Spatial relational memory requires hippocampal adult neurogenesis. PLoS One 2008;3:e1959.
[42] Farioli-Vecchioli S, Saraulli D, Costanzi M, Pacioni S, Cinà I, Aceti M, et al. The Timing of differentiation of adult hippocampal neurons is crucial for spatial memory. PLoS Biol 2008;6:e246.
[43] Garthe A, Behr J, Kempermann G. Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. PLoS One 2009;4:e5464.
[44] Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, et al. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 2008;11:1153–61.
[45] Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat Res 2004;162:39–47.
[46] Zhang C-L, Zou Y, He W, Gage FH, Evans RM. A role for adult TLX-positive neural stem cells in learning and behaviour. Nature 2008;451:1004–7.
[47] Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, Gould E. Neurogenesis in the adult is involved in the formation of trace memories. Nature 2001;410:372–6.
[48] Deng W, Saxe MD, Gallina IS, Gage FH. Adult-born hippocampal dentate granule cells undergoing maturation modulate learning and memory in the brain. J Neurosci 2009;29:13532–42.
[49] Jessberger S, Clark RE, Broadbent NJ, Clemenson GD, Consiglio A, Lie DC, et al. Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats. Learn Mem 2009;16:147–54.
[50] Saxe MD, Battaglia F, Wang J-W, Malleret G, David DJ, Monckton JE, et al. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci 2006;103: 17501–6.
[51] Shors TJ, Townsend DA, Zhao M, Kozorovitskiy Y, Gould E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 2002;12:578–84.
[52] Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM. A role for adult neurogenesis in spatial long-term memory. Neuroscience 2005;130:843–52.
[53] Saxe MD, Malleret G, Vronskaya S, Mendez I, Garcia AD, Sofroniew MV, et al. Paradoxical influence of hippocampal neurogenesis on working memory. Proc Natl Acad Sci 2007;104:4642–6.
[54] Jaholkowski P, Kiryk A, Jedynak P, Ben Abdallah NM, Knapska E, Kowalczyk A, et al. New hippocampal neurons are not obligatory for memory formation; cyclin D2 knockout mice with no adult brain neurogenesis show learning. Learn Mem 2009;16:439–51.
[55] Clelland CD, Choi M, Romberg C, Clemenson GD, Fragniere A, Tyers P, et al. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science 2009;325:210–3.
[56] Hernández-Rabaza V, Llorens-Martín M, Velázquez-Sánchez C, Ferragud A, Arcusa A, Gumus HG, et al. Inhibition of adult hippocampal neurogenesis disrupts contextual learning but spares spatial working memory, long-term conditional rule retention and spatial reversal. Neuroscience 2009;159: 59–68.
[57] Kitamura T, Saitoh Y, Takashima N, Murayama A, Niibori Y, Ageta H, et al. Adult neurogenesis modulates the hippocampus-dependent period of associative fear memory. Cell 2009;139:814–27.
[58] Tronel S, Belnoue L, Grosjean N, Revest J-M, Piazza P-V, Koehl M, et al. Adult-born neurons are necessary for extended contextual discrimination. Hippocampus 2010.
[59] Warner-Schmidt JL, Madsen TM, Duman RS. Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation. Eur J Neurosci 2008;27:1485–93.
[60] Winocur G, Wojtowicz JM, Sekeres M, Snyder JS, Wang S. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 2006;16:296–304.
[61] Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 2011;472:466–70.
[62] Jessberger S, Kempermann G. Adult-born hippocampal neurons mature into activity-dependent responsiveness. Eur J Neurosci 2003;18:2707–12.
[63] Ramirez-Amaya V, Marrone DF, Gage FH, Worley PF, Barnes CA. Integration of new neurons into functional neural networks. J Neurosci 2006;26:12237–41.
[64] Sandoval CJ, Martínez-Claros M, Bello-Medina PC, Pérez O, Ramírez-Amaya V. When are new hippocampal neurons, born in the adult brain, integrated into the network that processes spatial information? PLoS One 2011;6:e17689.
[65] Stone SSD, Teixeira CM, Zaslavsky K, Wheeler AL, Martinez-Canabal A, Wang AH, et al. Functional convergence of developmentally and adult-generated granule cells in dentate gyrus circuits supporting hippocampus-dependent memory. Hippocampus 2010.
[66] Tashiro A, Makino H, Gage FH. Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 2007;27:3252–9.
[67] Epp JR, Scott NA, Galea LAM. Strain differences in neurogenesis and activation of new neurons in the dentate gyrus in response to spatial learning. Neuroscience 2011;172:342–54.
[68] Aimone JB, Wiles J, Gage FH. Computational influence of adult neurogenesis on memory encoding. Neuron 2009;61:187–202.
[69] Alme CB, Buzzetti RA, Marrone DF, Leutgeb JK, Chawla MK, Schaner MJ, et al. Hippocampal granule cells opt for early retirement. Hippocampus 2010;20:1109–23.
[70] Trouche S, Bontempi B, Roullet P, Rampon C. Recruitment of adult-generated neurons into functional hippocampal networks contributes to updating and strengthening of spatial memory. Proc Natl Acad Sci 2009;106:5919–24.
[71] Kee N, Teixeira CM, Wang AH, Frankland PW. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 2007;10:355–62.