

Review

Adult Neurogenesis and Dendritic Remodeling in Hippocampal Plasticity: Which One Is More Important?

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Accumulating knowledge has shown that a decrease in hippocampal neurogenesis is linked to the pathophysiology of mood disorders and some hippocampal-dependent learning and memory tasks. The role of adult neurogenesis has initially been proposed based on correlations between decreases or increases in neurogenesis and impairments or improvements, respectively, in animal behaviors following interventions. Its role has been further elucidated through the ablation of neurogenesis. However, the functional roles of neurogenesis in hippocampal-dependent behaviors have been challenged by inconsistent findings between different studies. Despite the fact that factors affecting neurogenesis also induce dendritic or synaptic changes in newborn or existing neurons, these two aspects of structural changes within the hippocampus have always been examined separately. Thus, it is difficult to interpret the functional role of adult neurogenesis or dendritic remodeling in hippocampal-dependent behaviors. This review discusses the relative contribution of adult neurogenesis and dendritic/synaptic remodeling of existing neurons to hippocampal plasticity.

Key words: Hippocampal neurogenesis; Dendritic remodeling; Synaptic plasticity; Stress; Learning and memory; Voluntary running

INTRODUCTION

The discovery of adult neurogenesis in two neurogenic zones in the mammalian brain, the dentate gyrus and the subventricular zone, has provided hints on how functional recovery may occur in the central nervous system (CNS) following damages or how to improve brain plasticity in an aging population. The functional significance, regulation, and molecular mechanism of newborn neurons have been extensively investigated in the past decade with the aim of finding a therapeutic application of endogenous stem cells to regenerate the adult brain.

Stress and aging are associated with increased blood levels of glucocorticoids, reductions in adult neurogenesis, and impairments in learning and memory (22,30,69). Conversely, physical activity and environmental enrichment increase neurogenesis and improve performance

in hippocampal-dependent learning and memory tests (47,63,71). Reducing or blocking hippocampal neurogenesis disrupts various hippocampal-dependent learning and memory functions (52,56,66,67). Although a correlation between the number of newborn neurons and cognitive performance in animal behavioral studies has been demonstrated, inconsistencies among studies investigating the effects of ablation of adult neurogenesis have challenged the significance of hippocampal neurogenesis in learning and memory.

These discrepancies in the functional role of adult neurogenesis in the hippocampus may be attributed to numerous factors. These include different animal species and strains, ablation approaches and duration, and specificity of the behavioral tests. However, other aspects of neural changes (e.g., synaptic protein expression, spine density, dendrites, synapses) triggered by the same treatments have

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been neglected in most studies on hippocampal neurogenesis. It is difficult to interpret the relative contribution of adult neurogenesis or structural remodeling of existing neurons to hippocampal-dependent behaviors. To limit the focus of this review, the underlying molecular mechanisms of how neurogenesis, dendritic remodeling, and spine dynamics are regulated by external stimuli are not discussed. In this review, we mainly discuss the contribution of adult neurogenesis in the dentate region, dendritic remodeling, and synaptic strengthening of the existing neurons to hippocampal plasticity.

ADULT HIPPOCAMPAL NEUROGENESIS

Adult neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus. Synaptic remodeling of existing neurons in the hippocampus is known to be essential for hippocampal-dependent learning and memory formation. Adult hippocampal neurogenesis has been widely accepted as an important factor in modulation of hippocampal-dependent learning and memory (23,69); therefore, the integration of newborn neurons in the dentate gyrus serves as an additional plasticity in modifying existing neuronal circuitry in the adult hippocampus. The remodeling of the hippocampal structure may bring an important adaptive plasticity in response to different environmental challenges throughout life.

The hippocampus is defined as three major subregions based on the anatomical properties of glutamatergic

principal neurons within the hippocampus: dentate gyrus, CA3 and CA1 regions. The neural circuitry in the hippocampus is illustrated in Figure 1. The monosynaptic pathway involves direct projection from the entorhinal cortex to the CA1 or CA3 region for information processing, while the trisynaptic pathway involves axonal projection from the entorhinal cortex to the dentate gyrus where the outer and middle third of the dendritic tree are innervated by the axons from the lateral and medial entorhinal cortices. The dentate granular cells send projections to the pyramidal cells in the CA3 region through a mossy fiber pathway. The CA3 pyramidal neurons then send projections to the CA1 region via Schaffer collaterals. The projections finally go to the entorhinal cortex. Since adult neurogenesis occurs in the SGZ of the dentate gyrus, synaptic connections between the dentate gyrus and CA3 region via the mossy fiber tract can be modified by adult neurogenesis.

Newborn cells could receive functional synaptic inputs from the entorhinal cortex and local inhibitory neurons (31,64). Establishing axonal connection with pyramidal cells in the CA3 region rapidly within 4–10 days (1), the dendritic morphology of newborn cells becomes progressively more complex, and their neurites extend deeper into the granular cell layer during neuronal differentiation. With retroviral labeling of newborn cells with green fluorescent proteins, it has been demonstrated that new neurons form functional synaptic contact with their targets cells, including interneurons in hilus and pyramidal cells in the CA3 region by the third week of neuronal

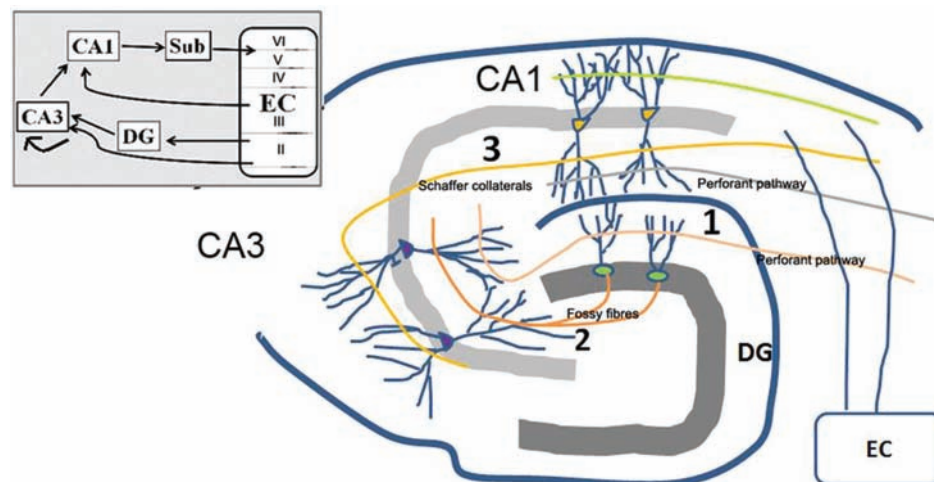


Figure 1. The synaptic circuitry of the hippocampus. Granular cells in the dentate gyrus are connected through three synaptic points (synapses 1–3). DG: dentate gyrus, EC: entorhinal cortex, Sub: subiculum. The trisynaptic pathway starts with the axonal projection from the entorhinal cortex layer II to the DG through the perforant pathway. The granular cells in the DG project to the CA3 region through mossy fibers. The CA3 pyramidal neurons send their projections to the CA1 region through Schaffer collaterals. CA1 pyramidal neurons send their axonal projection to the EC. In addition to the trisynaptic circuit, the CA3 pyramidal cells have an associative network interconnecting the pyramidal cell within this subregion. Furthermore, the entorhinal cortex sends projection directly to the CA3 and CA1 pyramidal cells. The CA3 pyramidal cells receive axonal projection from the layer II of the entorhinal cortex, whereas the CA1 pyramidal cells receive direct input from the layer III of the entorhinal cortex.

maturation (60). Immature neurons display enhanced synaptic plasticity in the adult hippocampus and demonstrate a lower threshold for long-term potentiation (LTP) induction in response to theta-burst stimulation (55). These immature neurons are characterized by more depolarized resting potentials and an increased LTP not seen in mature neurons. This may be due to the fact that γ -aminobutyric acid (GABA) is excitatory in immature neurons but is inhibitory around the time that excitatory glutamatergic synapses are established.

Elimination of new proliferating cells is very rapid if they are not incorporated into existing circuitry. Most newborn neurons are eliminated by cellular apoptosis (around 50–70% of new neurons die within the first month after division) (9); however, this process can be counteracted in an activity-dependent and survival-promoting manner. External stimuli, like exposure to physical activity, enriched environment, hippocampal-dependent learning, and antidepressant treatments have been shown to positively regulate the process of adult neurogenesis (12,40,47,48,63).

FUNCTIONS OF NEUROGENESIS IN LEARNING AND MEMORY

Details of how newborn neurons participate in the existing circuitry and modulate learning and memory are still unclear. Two computational models describing how neurogenesis affects memory formation in the hippocampus have been discussed by Deng et al. (10). One model is the replacement model, where newborn neurons continuously replace the existing neurons, which leads to the loss of old memories encoded by older neurons. The second model is the addition model, where neurogenesis enables new information to be effectively encoded while avoiding the interference of old information that has already been stored in the hippocampal network. These two models provide convergent evidence indicating the capability of newborn neurons to affect the functions of the dentate gyrus and therefore impact the functioning of the entire hippocampal circuit. As a result, a decrease or increase in hippocampal neurogenesis has substantial effects on hippocampal plasticity and hippocampal-dependent animal behavior (51,52). Studies from Garthe et al. have indicated that adult neurogenesis, with only a small number of new cells normally generated in the dentate gyrus, is likely involved in preventing memory interference from overlapping contexts rather than adding new information-processing functions to the hippocampus (18).

ADULT HIPPOCAMPAL NEUROGENESIS ON PATTERN SEPARATION

Pattern separation refers to the ability to separate similar parts of memories into distinct memory representations so as to avoid memory interference and confusion.

Pattern completion refers to the ability to retrieve a complete pattern of memory initiated by external cues. The role of newborn neurons in pattern separation, rather than a more generalized role in hippocampal-dependent learning and memory, has recently been discovered. This functional role of adult neurogenesis was initially illustrated by a lesion study showing that the dentate gyrus supports spatial pattern separation, whereas the CA1 region supports temporal pattern separation (19). In contrast, the CA3 region has been demonstrated to support pattern completion (46). Garthe et al. used a reversal protocol of the Morris water maze task and demonstrated that mice that had an inhibition of neurogenesis (through the use of the DNA-alkylating agent temozolomide) failed to identify the new position of the hidden platform and showed a significantly higher preference for the old position of the hidden platform (18). This study suggests that adult neurogenesis in the dentate gyrus is required to avoid memory interference from similar contexts, thus allowing efficient formation of new memories that are similar to previously acquired ones. Studies with ablation of adult neurogenesis by irradiation have further confirmed the role of adult neurogenesis on pattern separation. Mice with decreased levels of hippocampal neurogenesis show deficits in different spatial pattern separation tasks (7,61). These results raised the hypothesis that mice with increased neurogenesis may show improvement in spatial pattern separation. A recent study has indeed demonstrated that mice that have been exposed to voluntary wheel running demonstrate enhanced neurogenesis and enhanced spatial pattern separation (8). With a genetic tool to specifically enhance neurogenesis in the dentate gyrus, Sahay et al. have shown that mice with increased neurogenesis perform better in distinguishing between similar contextual representations in a behavioral paradigm of contextual fear discrimination learning. These findings suggest a positive relationship between pattern separation and neurogenesis (50).

The granular cell population is heterogeneous. Adult-born neurons constitute ~5%, and developmentally born neurons make up the remaining 95% of the neuronal population in the dentate gyrus (16,54). In transgenic mice with the dendritic output of specifically old granular cells inhibited by tetanus toxin and with intact 3- to 4-week-aged newborn neurons, it was found that young neurons are required for pattern separation, while old neurons are required for pattern completion in a rapid pattern completion-mediated memory recall (45). The authors hypothesized that the newborn neurons in the adult dentate gyrus undergo functional switches from pattern separation to rapid pattern completion when these new neurons aged. These data indicate that there is a distinct function of immature and mature subsets of granular cells in formation of new memories and recall of old memories.

A human study has recently shown that 6-week exercise training improved performance in a visual pattern separation task that is neurogenesis dependent, whereas an increase in depression scores negatively predicted the performance in visual pattern separation (11). Given the well-established positive effect of physical exercise and negative effect of stress on neurogenesis, this study has suggested that adult neurogenesis in the dentate region is likely involved in the improvement/deficit in pattern separation of human participants (11).

ACTIVITY-DEPENDENT SYNAPTIC PLASTICITY IN CA3–CA1 SYNAPSE FOLLOWING HIPPOCAMPAL-DEPENDENT LEARNING

Strengthening synaptic contact within hippocampal subregions is a form of enhanced synaptic efficacy. Experience-dependent changes in synaptic strength of CA3–CA1 synapse could occur during some form of hippocampal-dependent learning (24). Madronal et al. have shown that induction of LTP by high-frequency stimulation of the Schaffer collaterals 14 days before or during the classical eye blink conditioning learning task impairs the acquisition of the eye blink response, suggesting that disrupting the CA3–CA1 synaptic strength is sufficient to affect some form of associative learning process (37). Strengthening the synapse, which is activity dependent, has been shown to occur at the hippocampal CA3–CA1 synapse during different processes (acquisition, extinction, recall, and reconditioning) of a classical associative learning task of the conditioned eyelid responses (25). A recent study by Clarke et al. has demonstrated that object recognition memory consolidation was associated with transient potentiation in the hippocampal CA3–CA1 synapse. This study indicates that the synaptic strength of the hippocampal CA3–CA1 synapse is enhanced during the acquisition phase in an associative learning task (6). The authors showed that reactivation of a consolidated memory induced changes in CA3–CA1 synaptic efficacy, whereby reactivation of objection recognition memory (retrieval of a given memory that has already formed) triggered by a novel object induced synaptic modification in the hippocampus, suggesting that both memory consolidation and reconsolidation in the phase of memory formation is capable of modifying hippocampal plasticity. This may imply that strengthening of the synapse could occur during the process of pattern separation and pattern completion in the CA3–CA1 synapse. It warrants further study to examine whether a similar change of synaptic strength occurs in the dentate gyrus during the process of pattern separation, as this region has been suggested to be responsible for spatial pattern separation as discussed above. Given the above evidence, it is clear that

strengthening synaptic contact in the CA3–CA1 synapse following learning can contribute to enhanced synaptic plasticity in the hippocampus.

DENDRITIC REMODELING IN RELATION TO LEARNING AND MEMORY

Dendritic remodeling of the existing neurons has been shown to be correlated with learning and memory. Physical exercise and stress exert opposite effects on dendritic remodeling of hippocampal neurons. Voluntary running in rodents induces dendritic remodeling in the dentate gyrus, CA1, and entorhinal cortex (58). Animals with running show increased spine density and increased dendritic complexity in terms of increase in cell proportion with one to two primary dendrites and overall dendritic length (49). Furthermore, enhancement of spine density in the dentate region has been reported in animals following 2 weeks of running (20). Running improves learning and memory in association with enhanced LTP and neurogenesis in the dentate region (62). In addition, running enhances the number of mushroom spines in newborn neurons, indicating enhanced spine maturation (64). Conversely, chronic exposure to unpredictable stress is known to suppress the induction of LTP not only in the dentate regions but also in the CA1 region (2). Stress or exogenous corticosterone application primarily induces dendritic atrophy in the apical dendrites of the CA3 regions. Severe dendritic retraction in the CA3 area has repeatedly been reported in various animal species with different stress paradigms, like prolonged corticosterone treatment, chronic restraint stress, and the psychosocial stress model (39,65,68). Stress causes dendritic atrophy as indicated by decrease in the number and length of branch points of the CA3 apical dendrites. Dendritic atrophy in the CA3 region may negatively affect the dendritic projection to CA1 from CA3 region, which could lead to impaired hippocampal function and behavioral deficits, such as impairments in hippocampal-dependent learning and memory.

Prenatal stress impairs spatial learning in the Morris water maze and decreases the length and number of dendritic segments and branching in the CA3 region and dentate gyrus, but not in the CA1 region (27). Exposure to 7 days of hypobaric hypoxia induces a significant decrease in dendritic branching and length in the CA1 region in association with severe learning deficit in the partially baited radial arm maze task (59). In contrast, Lopes et al. observed no impairment in spatial learning and memory in the Morris water maze test though they observed significant dendritic atrophy in the CA3 region of the adult offspring with gestational protein restriction (36). The CA3 region is known to be essential for acquisition and memory consolidation in the Morris water maze task in mice (17). Therefore, it is possible that another form of

plasticity (e.g., alteration in the levels of neurogenesis) may play a role in compensating for the atrophy that occurred in the subregions of the hippocampus.

INTERPLAY BETWEEN NEWBORN NEURONS AND DENDRITIC REMODELING IN HIPPOCAMPAL FUNCTION

Approaches of ablating neurogenesis have commonly been used as a direct investigation of the functions of neurogenesis in cognitive performance. Several methods, including antimetabolic drug administration, irradiation, and genetic intervention, have been used to suppress the production of new neurons in the adult brain to study their involvement in learning and memory. Injection with a DNA-methylating agent [methylazoxymethanol (MAM)] or irradiation significantly reduces hippocampal neurogenesis (51,57). However, these two approaches block hippocampal neurogenesis nonspecifically and induce side effects that may cause detrimental effects on brain physiology and function. For example, irradiation may inhibit cell proliferation and damage the stem cell niche (43).

With advanced research techniques, a more specific and noninvasive genetic approach has been applied to block proliferation of neural progenitors. However, divergent results are still apparent. In transgenic mice expressing the herpes virus thymidine kinase in glial fibrillary acidic protein (GFAP)-positive progenitor cells in all neurogenic brain regions, proliferating thymidine kinase cells are killed after oral delivery of the antiviral prodrug gancyclovir. Saxe et al. showed that neurogenesis ablation did not alter normal spatial memory but impaired contextual fear conditioning (52). Dupret and colleagues blocked nestin-positive neural precursors in mice by using the reverse tetracycline-controlled transactivator regulatory system to overexpress proapoptotic protein B-cell CLL/lymphoma 2 (BCL2)-associated X protein (Bax) in the nestin-positive neural precursors (14). This group demonstrated that ablation of adult neurogenesis in mice results in deficit in spatial learning and memory in the Morris water maze test but not fear-conditioned learning. This observation is consistent with the finding from Zhang and colleagues using the ablation method of inducible removal of the orphan nuclear receptor tailless-related receptor (TLX) (72). Taken together, these findings may suggest that adult hippocampal neurogenesis may be involved in specific types of hippocampal-dependent behavior.

Newborn neurons exhibit not only enhanced plasticity but also preferential activation during spatial exploration and hippocampal-dependent spatial learning and primary reactivation during memory recall (28). Indeed, Schinder and Gage have proposed that neurogenesis may complement synaptic plasticity and memory function of older

neurons and consequently may increase learning capability (53). In addition to adult neurogenesis, dendritic remodeling and synaptic changes should be considered as taking part in the modulation of hippocampal functions as these structural changes confer adaptive plasticity in response to environmental stimuli (35). However, because factors that affect neurogenesis also induce structural remodeling of the existing neurons, it is difficult to clearly interpret the functions of adult neurogenesis in hippocampal-dependent learning and memory.

Negative regulators of adult neurogenesis include stress or high levels of glucocorticoids, which have been shown to cause dendritic retraction of CA3 pyramidal neurons and loss of dendritic spine in adult male rats and tree shrews (39,41). Furthermore, exposure to chronic stress induces dendritic atrophy and spine loss in the dentate gyrus and CA1 (26). In contrast to stress, environmental enrichment, physical exercise (in terms of running), and hippocampal-dependent learning show beneficial effects on inducing both adult neurogenesis and dendritic remodeling in the hippocampus (12,15,34,48,58). A variety of hippocampal-dependent learning, like the associative learning task in trace eye blink conditioning and spatial learning in the Morris water maze task, increases neurogenesis in the dentate gyrus (3,13,21). Electrophysiological studies show that increased synaptic activity (represented by an enhancement in LTP) increases cell proliferation and cell survival (5). Furthermore, learning itself also changes spine number and morphology (29,44). Despite the fact that both adult neurogenesis and dendritic remodeling in the existing neurons play an important role in hippocampal function, these two aspects have normally been examined separately in the literature.

Changes in hippocampal neurogenesis and dendritic modification occur simultaneously following exposure to stress or physical exercise (Fig. 2). It is unclear which modification has a greater impact on hippocampal plasticity. Yau et al. used an animal model of stress with voluntary running to examine whether neurogenesis or dendritic remodeling has a greater influence on hippocampal functions (70). This study observed that running improved depression-like behavior and spatial learning in association with restored hippocampal neurogenesis, spine density, and enhanced dendritic complexity in corticosterone-treated rats (an animal model of stress). Blockade of neurogenesis with an antimetabolic drug, cytosine arabinoside (Ara-c), diminished the counteractive effect of running on stress, despite the enhancement in dendritic complexity and spine density in the CA3 region of these rats. Conversely, blockade of neurogenesis in normal (nonstress) rats exhibiting enhanced dendritic length and spine density in CA3 pyramidal cells shows no behavioral changes following running. Yau et al. hypothesized that under normal conditions, enhancement

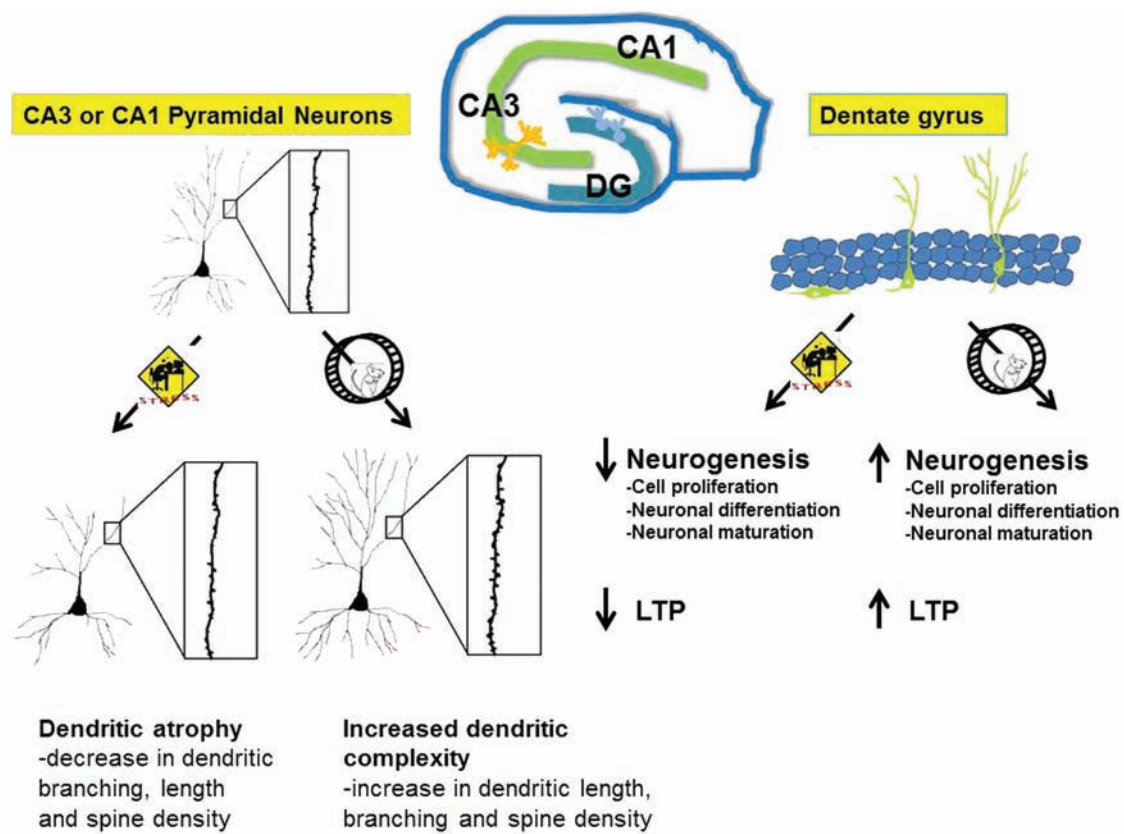


Figure 2. Simultaneous modulation of dendritic complexity, synaptic plasticity, and neurogenesis in the hippocampus by a representative negative regulator (stress) and a positive regulator (physical exercise). LTP: long-term potentiation.

in dendritic remodeling may play a compensatory role in maintaining the integration of hippocampal circuitry and thus may be sufficient to maintain hippocampal function and prevent behavioral deficits in the absence of adult neurogenesis. Conversely, under pathological conditions, like stress, both adult neurogenesis and dendritic remodeling are required for maintaining intact hippocampal function, which may, in turn, enable animals to overcome the stress-induced effects on behavior.

Madronal et al. have demonstrated that animals exposed to physically enriched environments and to social enrichment did not display differences in hippocampal neurogenesis. Improvements in motor performance and operant conditioning are only observed in animals with enriched physical environments (38). In this study, social interaction increased neurogenesis but did not affect learning ability, suggesting that the physical factor may be important for the behavioral improvement observed in this study. This may be due to the fact that physical activity simultaneously increases neurogenesis and dendritic plasticity in the hippocampus in the animals with a physically enriched environment, but not in the animals with socially enriched environments. The authors argued that an alteration in

neurogenesis is not always required for a change in animal behavior, as social interaction increases neurogenesis and cell proliferation, but did not improve hippocampal-dependent spatial learning abilities in their study. Their speculation is supported by a study showing that improvement in spatial learning in animals with enriched environment is independent of an increase in hippocampal neurogenesis (42).

No behavioral changes have been found in normal animals with neurogenesis ablation by antimetabolic drug or irradiation (56,67). However, dendritic or synaptic remodeling of existing neurons has not yet been examined in these animals. It is possible that some forms of compensation from existing neurons may occur in the absence of newborn neurons in normal animals, thus maintaining hippocampal neuronal connectivity and preventing behavioral deficits in animals without newborn neurons (70). In a rat model of chronic unpredictable stress, antidepressants improve depressive behavior in a neurogenesis-independent manner and in association with dendritic remodeling in the prefrontal cortex and hippocampus (4). Furthermore, in a rat model of depression induced by chronic treatment with 50 mg/kg corticosterone, the antidepressant effect of a

Chinese herbal medicine named Wolfberry has been shown to be mediated through an enhancement of synaptic plasticity (increased protein expression of synaptic proteins) in spite of no changes in hippocampal neurogenesis following treatment (73). These studies may suggest that enhanced dendritic/synaptic plasticity may be substantial for maintaining hippocampal function and hence exert antidepressant effects in some situations.

CONCLUSION

Although different methods for ablating neurogenesis have been applied to elucidate the functional involvement of neurogenesis in some hippocampal-dependent behaviors, interventions that also affect the dendritic and synaptic remodeling of the existing neurons should be taken into account before concluding the functional role of neurogenesis in hippocampal-dependent animal behaviors. Adult neurogenesis in the dentate gyrus and structural remodeling in the CA1 or CA3 regions may interact with each other. This may lead to a compensatory effect on sub-region-specific deficits, such that an intact hippocampal circuitry may be maintained in spite of dendritic atrophy or a decrease in neurogenesis. It is difficult to manipulate neurogenesis without affecting other factors following treatment, like physical exercise, antidepressant therapy, and environment enrichment. In such circumstances, the functional role of adult neurogenesis in hippocampal-dependent behaviors is hard to elucidate. An accurate conclusion on the functional role of adult neurogenesis or structural remodeling within the hippocampus may only be made when other potential confounding variables can be ruled out. As suggested by Lazic, the neurogenesis-independent effect on behavior should be measured or taken into consideration when performing data analysis of neurogenesis and behavioral correlations (32,33).

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REFERENCES

1. Abrous, D. N.; Koehl, M.; Le Moal, M. Adult neurogenesis: From precursors to network and physiology. *Physiol. Rev.* 85(2):523–569; 2005.
2. Alfarez, D. N.; Joels, M.; Krugers, H. J. Chronic unpredictable stress impairs long-term potentiation in rat hippocampal CA1 area and dentate gyrus in vitro. *Eur. J. Neurosci.* 17(9):1928–1934; 2003.
3. Ambrogini, P.; Cuppini, R.; Cuppini, C.; Ciaroni, S.; Cecchini, T.; Ferri, P.; Sartini, S.; Del Grande, P. Spatial learning affects immature granule cell survival in adult rat dentate gyrus. *Neurosci. Lett.* 286(1):21–24; 2000.
4. Bessa, J. M.; Ferreira, D.; Melo, I.; Marques, F.; Cerqueira, J. J.; Palha, J. A.; Almeida, O. F.; Sousa, N. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Mol. Psychiatry* 14(8):764–773; 2009.
5. Bruel-Jungerman, E.; Davis, S.; Rampon, C.; Laroche, S. Long-term potentiation enhances neurogenesis in the adult dentate gyrus. *J. Neurosci.* 26(22):5888–5893; 2006.
6. Clarke, J. R.; Cammarota, M.; Gruart, A.; Izquierdo, I.; Delgado-Garcia, J. M. Plastic modifications induced by object recognition memory processing. *Proc. Natl. Acad. Sci. USA* 107(6):2652–2657; 2010.
7. Clelland, C. D.; Choi, M.; Romberg, C.; Clemenson, G. D., Jr.; Fragniere, A.; Tyers, P.; Jessberger, S.; Saksida, L. M.; Barker, R. A.; Gage, F. H.; Bussey, T. J. A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 325(5937):210–213; 2009.
8. Creer, D. J.; Romberg, C.; Saksida, L. M.; van Praag, H.; Bussey, T. J. Running enhances spatial pattern separation in mice. *Proc. Natl. Acad. Sci. USA* 107(5):2367–2372; 2010.
9. Dayer, A. G.; Ford, A. A.; Cleaver, K. M.; Yassae, M.; Cameron, H. A. Short-term and long-term survival of new neurons in the rat dentate gyrus. *J. Comp. Neurol.* 460(4):563–572; 2003.
10. Deng, W.; Aimone, J. B.; Gage, F. H. New neurons and new memories: How does adult hippocampal neurogenesis affect learning and memory? *Nat. Rev. Neurosci.* 11(5):339–350; 2010.
11. Dery, N.; Pilgrim, M.; Gibala, M.; Gillen, J.; Wojtowicz, J. M.; Macqueen, G.; Becker, S. Adult hippocampal neurogenesis reduces memory interference in humans: Opposing effects of aerobic exercise and depression. *Front. Neurosci.* 7:66; 2013.
12. Dobrossy, M. D.; Drapeau, E.; Auroousseau, C.; Le Moal, M.; Piazza, P. V.; Abrous, D. N. Differential effects of learning on neurogenesis: Learning increases or decreases the number of newly born cells depending on their birth date. *Mol. Psychiatry* 8(12):974–982; 2003.
13. Dupret, D.; Fabre, A.; Dobrossy, M. D.; Panatier, A.; Rodriguez, J. J.; Lamarque, S.; Lemaire, V.; Olier, S. H.; Piazza, P. V.; Abrous, D. N. Spatial learning depends on both the addition and removal of new hippocampal neurons. *PLoS Biol.* 5(8):e214; 2007.
14. Dupret, D.; Revest, J. M.; Koehl, M.; Ihas, F.; De Giorgi, F.; Costet, P.; Abrous, D. N.; Piazza, P. V. Spatial relational memory requires hippocampal adult neurogenesis. *PLoS One* 3(4):e1959; 2008.
15. Eadie, B. D.; Redila, V. A.; Christie, B. R. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J. Comp. Neurol.* 486(1):39–47; 2005.
16. Eriksson, P. S.; Perfilieva, E.; Bjork-Eriksson, T.; Alborn, A. M.; Nordborg, C.; Peterson, D. A.; Gage, F. H. Neurogenesis in the adult human hippocampus. *Nat. Med.* 4(11):1313–1317; 1998.
17. Florian, C.; Roulet, P. Hippocampal CA3-region is crucial for acquisition and memory consolidation in Morris water maze task in mice. *Behav. Brain Res.* 154(2):365–374; 2004.
18. Garthe, A.; Behr, J.; Kempermann, G. Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. *PLoS One* 4(5):e5464; 2009.
19. Gilbert, P. E.; Kesner, R. P.; Lee, I. Dissociating hippocampal subregions: Double dissociation between dentate gyrus and CA1. *Hippocampus* 11(6):626–636; 2001.
20. Glasper, E. R.; Llorens-Martin, M. V.; Leuner, B.; Gould, E.; Trejo, J. L. Blockade of insulin-like growth factor-I has complex effects on structural plasticity in the hippocampus. *Hippocampus* 20(6):706–712; 2010.

21. Gould, E.; Beylin, A.; Tanapat, P.; Reeves, A.; Shors, T. J. Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.* 2(3):260–265; 1999.
22. Gould, E.; Cameron, H. A.; Daniels, D. C.; Woolley, C. S.; McEwen, B. S. Adrenal hormones suppress cell division in the adult rat dentate gyrus. *J. Neurosci.* 12(9):3642–3650; 1992.
23. Gould, E.; Tanapat, P.; Hastings, N. B.; Shors, T. J. Neurogenesis in adulthood: A possible role in learning. *Trends Cogn. Sci.* 3(5):186–192; 1999.
24. Gruart, A.; Delgado-Garcia, J. M. Activity-dependent changes of the hippocampal CA3-CA1 synapse during the acquisition of associative learning in conscious mice. *Genes Brain Behav.* 6(Suppl 1):24–31; 2007.
25. Gruart, A.; Munoz, M. D.; Delgado-Garcia, J. M. Involvement of the CA3-CA1 synapse in the acquisition of associative learning in behaving mice. *J. Neurosci.* 26(4):1077–1087; 2006.
26. Hajszan, T.; Dow, A.; Warner-Schmidt, J. L.; Szigeti-Buck, K.; Sallam, N. L.; Parducz, A.; Leranth, C.; Duman, R. S. Remodeling of hippocampal spine synapses in the rat learned helplessness model of depression. *Biol. Psychiatry* 65(5):392–400; 2009.
27. Hosseini-Sharifabad, M.; Hadinedoushan, H. Prenatal stress induces learning deficits and is associated with a decrease in granules and CA3 cell dendritic tree size in rat hippocampus. *Anat. Sci. Int.* 82(4):211–217; 2007.
28. Kee, N.; Teixeira, C. M.; Wang, A. H.; Frankland, P. W. Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nat. Neurosci.* 10(3):355–362; 2007.
29. Knafo, S.; Ariav, G.; Barkai, E.; Libersat, F. Olfactory learning-induced increase in spine density along the apical dendrites of CA1 hippocampal neurons. *Hippocampus* 14(7):819–825; 2004.
30. Kuhn, H. G.; Dickinson-Anson, H.; Gage, F. H. Neurogenesis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. *J. Neurosci.* 16(6):2027–2033; 1996.
31. Laplagne, D. A.; Esposito, M. S.; Piatti, V. C.; Morgenstern, N. A.; Zhao, C.; van Praag, H.; Gage, F. H.; Schinder, A. F. Functional convergence of neurons generated in the developing and adult hippocampus. *PLoS Biol.* 4(12):e409; 2006.
32. Lazic, S. E. Relating hippocampal neurogenesis to behavior: The dangers of ignoring confounding variables. *Neurobiol. Aging* 31(12):2169–2171; discussion 2172–2175; 2010.
33. Lazic, S. E. Using causal models to distinguish between neurogenesis-dependent and -independent effects on behaviour. *J. R. Soc. Interface* 9(70):907–917; 2012.
34. Leuner, B.; Falduto, J.; Shors, T. J. Associative memory formation increases the observation of dendritic spines in the hippocampus. *J. Neurosci.* 23(2):659–665; 2003.
35. Leuner, B.; Gould, E. Structural plasticity and hippocampal function. *Annu. Rev. Psychol.* 61:111–140; 2010.
36. Lopes, A.; Torres, D. B.; Rodrigues, A. J.; Cerqueira, J. J.; Pego, J. M.; Sousa, N.; Gontijo, J. A.; Boer, P. A. Gestational protein restriction induces CA3 dendritic atrophy in dorsal hippocampal neurons but does not alter learning and memory performance in adult offspring. *Int. J. Dev. Neurosci.* 31(3):151–156; 2013.
37. Madronal, N.; Delgado-Garcia, J. M.; Gruart, A. Differential effects of long-term potentiation evoked at the CA3 CA1 synapse before, during, and after the acquisition of classical eye blink conditioning in behaving mice. *J. Neurosci.* 27(45):12139–12146; 2007.
38. Madronal, N.; Lopez-Aracil, C.; Rangel, A.; del Rio, J. A.; Delgado-Garcia, J. M.; Gruart, A. Effects of enriched physical and social environments on motor performance, associative learning, and hippocampal neurogenesis in mice. *PLoS One* 5(6):e11130; 2010.
39. Magarinos, A. M.; McEwen, B. S.; Flugge, G.; Fuchs, E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. *J. Neurosci.* 16(10):3534–3540; 1996.
40. Malberg, J. E.; Eisch, A. J.; Nestler, E. J.; Duman, R. S. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* 20(24):9104–9110; 2000.
41. McKittrick, C. R.; Magarinos, A. M.; Blanchard, D. C.; Blanchard, R. J.; McEwen, B. S.; Sakai, R. R. Chronic social stress reduces dendritic arbors in CA3 of hippocampus and decreases binding to serotonin transporter sites. *Synapse* 36(2):85–94; 2000.
42. Meshi, D.; Drew, M. R.; Saxe, M.; Ansorge, M. S.; David, D.; Santarelli, L.; Malapani, C.; Moore, H.; Hen, R. Hippocampal neurogenesis is not required for behavioral effects of environmental enrichment. *Nat. Neurosci.* 9(6):729–731; 2006.
43. Monje, M. L.; Mizumatsu, S.; Fike, J. R.; Palmer, T. D. Irradiation induces neural precursor-cell dysfunction. *Nat. Med.* 8(9):955–962; 2002.
44. Moser, M. B.; Trommald, M.; Andersen, P. An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. *Proc. Natl. Acad. Sci. USA* 91(26):12673–12675; 1994.
45. Nakashiba, T.; Cushman, J. D.; Pelkey, K. A.; Renaudineau, S.; Buhl, D. L.; McHugh, T. J.; Rodriguez Barrera, V.; Chittajallu, R.; Iwamoto, K. S.; McBain, C. J.; Fanselow, M. S.; Tonegawa, S. Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 149(1):188–201; 2012.
46. Nakashiba, T.; Young, J. Z.; McHugh, T. J.; Buhl, D. L.; Tonegawa, S. Transgenic inhibition of synaptic transmission reveals role of CA3 output in hippocampal learning. *Science* 319(5867):1260–1264; 2008.
47. Nilsson, M.; Perfilieva, E.; Johansson, U.; Orwar, O.; Eriksson, P. S. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *J. Neurobiol.* 39(4):569–578; 1999.
48. Olson, A. K.; Eadie, B. D.; Ernst, C.; Christie, B. R. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. *Hippocampus* 16(3):250–260; 2006.
49. Redila, V. A.; Christie, B. R. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience* 137(4):1299–1307; 2006.
50. Sahay, A.; Scobie, K. N.; Hill, A. S.; O'Carroll, C. M.; Kheirbek, M. A.; Burghardt, N. S.; Fenton, A. A.; Dranovsky, A.; Hen, R. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature* 472(7344):466–470; 2011.
51. Santarelli, L.; Saxe, M.; Gross, C.; Surget, A.; Battaglia, F.; Dulawa, S.; Weisstaub, N.; Lee, J.; Duman, R.; Arancio, O.; Belzung, C.; Hen, R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301(5634):805–809; 2003.

52. Saxe, M. D.; Battaglia, F.; Wang, J. W.; Malleret, G.; David, D. J.; Monckton, J. E.; Garcia, A. D.; Sofroniew, M. V.; Kandel, E. R.; Santarelli, L.; Hen, R.; Drew, M. R. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc. Natl. Acad. Sci. USA* 103(46):17501–17506; 2006.
53. Schinder, A. F.; Gage, F. H. A hypothesis about the role of adult neurogenesis in hippocampal function. *Physiology* 19:253–261; 2004.
54. Schlessinger, A. R.; Cowan, W. M.; Gottlieb, D. I. An autoradiographic study of the time of origin and the pattern of granule cell migration in the dentate gyrus of the rat. *J. Comp. Neurol.* 159(2):149–175; 1975.
55. Schmidt-Hieber, C.; Jonas, P.; Bischofberger, J. Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. *Nature* 429(6988):184–187; 2004.
56. Shors, T. J.; Townsend, D. A.; Zhao, M.; Kozorovitskiy, Y.; Gould, E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus* 12(5):578–584; 2002.
57. Snyder, J. S.; Hong, N. S.; McDonald, R. J.; Wojtowicz, J. M. A role for adult neurogenesis in spatial long-term memory. *Neuroscience* 130(4):843–852; 2005.
58. Stranahan, A. M.; Khalil, D.; Gould, E. Running induces widespread structural alterations in the hippocampus and entorhinal cortex. *Hippocampus* 17(11):1017–1022; 2007.
59. Titus, A. D.; Shankaranarayana Rao, B. S.; Harsha, H. N.; Ramkumar, K.; Srikumar, B. N.; Singh, S. B.; Chattarji, S.; Raju, T. R. Hypobaric hypoxia-induced dendritic atrophy of hippocampal neurons is associated with cognitive impairment in adult rats. *Neuroscience* 145(1):265–278; 2007.
60. Toni, N.; Laplagne, D. A.; Zhao, C.; Lombardi, G.; Ribak, C. E.; Gage, F. H.; Schinder, A. F. Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat. Neurosci.* 11(8):901–907; 2008.
61. Tronel, S.; Belnoue, L.; Grosjean, N.; Revest, J. M.; Piazza, P. V.; Koehl, M.; Abrous, D. N. Adult-born neurons are necessary for extended contextual discrimination. *Hippocampus* 22(2):292–298; 2012.
62. van Praag, H.; Christie, B. R.; Sejnowski, T. J.; Gage, F. H. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. USA* 96(23):13427–13431; 1999.
63. van Praag, H.; Kempermann, G.; Gage, F. H. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2(3):266–270; 1999.
64. van Praag, H.; Schinder, A. F.; Christie, B. R.; Toni, N.; Palmer, T. D.; Gage, F. H. Functional neurogenesis in the adult hippocampus. *Nature* 415(6875):1030–1034; 2002.
65. Watanabe, Y.; Gould, E.; McEwen, B. S. Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res.* 588(2):341–345; 1992.
66. Winocur, G.; Wojtowicz, J. M.; Sekeres, M.; Snyder, J. S.; Wang, S. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. *Hippocampus* 16(3):296–304; 2006.
67. Wojtowicz, J. M.; Askew, M. L.; Winocur, G. The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *Eur. J. Neurosci.* 27(6):1494–1502; 2008.
68. Woolley, C. S.; Gould, E.; McEwen, B. S. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res.* 531(1–2):225–231; 1990.
69. Yau, S. Y.; Lau, B. W.; So, K. F. Adult hippocampal neurogenesis: A possible way how physical exercise counteracts stress. *Cell Transplant.* 20(1):99–111; 2011.
70. Yau, S. Y.; Lau, B. W.; Tong, J. B.; Wong, R.; Ching, Y. P.; Qiu, G.; Tang, S. W.; Lee, T. M.; So, K. F. Hippocampal neurogenesis and dendritic plasticity support running-improved spatial learning and depression-like behaviour in stressed rats. *PLoS One* 6(9):e24263; 2011.
71. Yau, S. Y.; Lau, B. W.; Zhang, E. D.; Lee, J. C.; Li, A.; Lee, T. M.; Ching, Y. P.; Xu, A. M.; So, K. F. Effects of voluntary running on plasma levels of neurotrophins, hippocampal cell proliferation and learning and memory in stressed rats. *Neuroscience* 222:289–301; 2012.
72. Zhang, C. L.; Zou, Y.; He, W.; Gage, F. H.; Evans, R. M. A role for adult TLX-positive neural stem cells in learning and behaviour. *Nature* 451(7181):1004–1007; 2008.
73. Zhang, E.; Yau, S. Y.; Wui Man Lau, B.; Ma, H.; Lee, T. M.; Chuen-Chung Chang, R.; So, K. F. Synaptic plasticity, but not hippocampal neurogenesis, mediated the counteractive effect of wolfberry on depression in rats. *Cell Transplant.* 21(12):2635–2649; 2012.