Adult neurogenesis has been highly conserved throughout evolution; it has been observed in the central nervous systems of invertebrates and vertebrates such as fish, birds, and mammals (1, 5, 10, 26). Most studies carried out under physiological conditions in adult mammals indicate that significant levels of neurogenesis occur exclusively in the dentate gyrus of the hippocampus (DG; FIGURE 1) and the olfactory bulb (OB). In the adult human brain, neurogenesis has been detected in the DG (9), but no evidence of adult-born neurons has yet been found in the OB (35).

Newly generated neurons derive from multipotent neural progenitor cells (NPCs) that proliferate, migrate, and differentiate into specific neuronal phenotypes (10). It is very striking that, whereas NPCs are highly ubiquitous in the adult brain, neurogenesis remains very much restricted to the subgranular zone (SGZ) of the DG and the subventricular zone of the lateral ventricles (SVZ). The SGZ and SVZ give rise primarily to dentate granule cells (DGCs; FIGURE 1) and interneurons of the OB, respectively (1, 10). Growing evidence indicates that new neurons become functionally integrated in the existing circuits (2, 4, 16, 39, 52), although the true physiological relevance of adult neurogenesis remains unknown.

The spatial restriction observed in adult neurogenesis suggests that most regions of the adult brain may not require new neurons for their normal function. Therefore, at least two possibilities emerge: 1) that the adult brain shuts off neurogenesis and what is left during adulthood is a remnant of development without physiological significance; or 2) that neurogenesis is required for a very specific set of brain functions that are concentrated primarily in the hippocampus and OB. If the latter were true, those specific functions are yet to be discovered. Increasing evidence suggests that neurogenesis may play a key role in olfactory processing in the adult brain (6, 11, 33, 40). A thorough review of this topic has been recently published (18), and therefore this review will focus on the putative functional role of newly generated neurons in the adult mammalian hippocampus. We will discuss current data in the context of a plausible hypothesis that describes how new neurons could modify hippocampal function. The proposed hypothesis exploits the notion that adult neurogenesis might serve as a powerful mechanism for plasticity of brain circuits.

A Hypothesis About the Functional Role of Neurogenesis in the Adult Hippocampus

It has long been known that hippocampal formation is involved in certain forms of learning and memory. The discovery of adult hippocampal neurogenesis has led to the notion that new neurons might play a critical role in learning and memory processing (13). However, the precise role of new neurons in hippocampal function has not been thoroughly analyzed, and fundamental questions remain unanswered: Why would adult hippocampal functions require neurogenesis? How would new cells be different from mature neurons? What functional modifications would be impinged by new neurons in the hippocampal network?

Similar questions emerged about 30 years ago in studies seeking to relate synaptic plasticity to learning and memory. It is useful to provide here an accepted definition of memory as explained by Dudai (8): “Memories are experience-dependent internal representations, in other words, acquired models of the world, encoded in the spatiotemporal activity of brain circuits. Their use-dependent change is probably made possible by synaptic plasticity.” This idea was formalized by Martin and Morris (22) in the “synaptic plasticity and memory” (SPM) hypothesis, in which they propose that “activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and it is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plastic-

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ity is observed." In this context, synaptic plasticity refers to different forms of activity-dependent modification of synaptic efficacy, which might include some elements such as those described for long-term potentiation (LTP) and depression (LTD). The SPM hypothesis, which is becoming widely accepted, took about three decades and literally hundreds of papers and myriad approaches to develop (22).

The hypothesis for functional neurogenesis discussed in this paper proposes that hippocampus-dependent learning involves recruitment of newly generated neurons into the existing circuits of the DG, such that new neurons play a central role in the processing, storage, and/or retrieval of new memories. The way in which experience shapes circuits might be by promoting synaptogenesis to enhance further functional integration of new neurons or by changing the efficacy of existing synapses formed between new and mature neurons of the hippocampal circuits (FIGURE 2). Whether or not adult neurogenesis is part of the SPM hypothesis is discussed below.

Requirements of the hypothesis
1. New cells must be functionally integrated in the circuits. For the hypothesis to be viable at all, new neurons must become part of the neuronal network that is involved in the learning process (in this case, the DG of the hippocampus). Functional integration demands a developmental program to express full neuronal function, including the following:
   a) maturation of neuronal excitability,
   b) synaptogenesis at postsynaptic sites,
   c) synaptogenesis at axonal projections, and
   d) synthesis and release of neurotransmitters.

2. Learning requires neurogenesis. The relationship between learning and neurogenesis can be fairly complex. The requirement considered here is for a basal level of neurogenesis that allows learning to take place, regardless of whether or not an increase in neurogenesis will improve learning or whether learning will increase neurogenesis.

3. New cells participate in memory storage or learning. If new cells participate in the network where new memories are stored, their selective destruction should erase such memories (prediction 1). If new cells are involved in the
learning process but not in memory storage, then lack of basal neurogenesis should impair learning (prediction II). However, the memory of the event should remain intact if new neurons are killed only after memory formation (prediction III). In either case, the substrate for memory should involve connections formed between the existing circuits and the newly generated neurons.

**Physiological role for new neurons**

To propose a specific role for new neurons, it is important to define whether such a role relates to the SPM hypothesis, i.e., whether the role of neurogenesis is linked to an improvement in the plasticity of synaptic connections (FIGURE 2). Some non-mutually exclusive alternatives are as follows:

1. Neurogenesis increases synaptic plasticity. Here the main contribution of newly generated neurons to the existing circuits is to generate synapses with a higher degree of plasticity. Learning could, for example, induce changes in the efficacy at a subset of synapses that involve new neurons at the pre- or postsynaptic sites. Increased plasticity could be expressed as a lower threshold for synaptic potentiation and/or depression, larger or longer-lasting changes in synaptic efficacy, etc. If so, synapses formed onto or by newly generated neurons should display a higher plasticity than those of mature DGCs.

2. Neurogenesis produces neurons with unique physiological properties. Newly generated neurons might process incoming information in a form that is different from the mature DGCs but not linked to changes in synaptic plasticity. This distinction may reside at the level of inputs, signal integration, and/or output. Possibilities include a different transmitter phenotype for newly generated neurons (GABAergic instead of glutamatergic) or different schemes of network connectivity.

3. New neurons contribute with a renewed pool of connections with physiological properties that are similar to those of mature DGCs. Newly born neurons and mature neurons could have similar

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**FIGURE 2. Neurogenesis and the synaptic plasticity and memory hypothesis**

Hypothetical pathways from neurogenesis to memory are shown. The synaptic plasticity and memory (SPM) hypothesis proposes that activation of existing neurons (generated during development) induces plasticity at specific connections that are relevant for formation, storage, or retrieval of memory (purple path). We propose the following three additional options where neurogenesis can contribute to learning and memory in the context of the SPM hypothesis. Experience may activate synapses formed onto or by newly generated neurons that have higher levels of plasticity (green path); learning may induce the recruitment of immature neurons that are ready to connect by promoting synaptogenesis or spiking activity, thus allowing the neuron to integrate to the existing circuits (gold path); or a basal rate of neurogenesis may replace old, dying neurons. It might take several weeks before a new neuron is mature enough to play a relevant functional role (blue path). In principle, all of these pathways may coexist.
intrinsic physiology, plasticity, and connectivity. The central role here would be to renew synapses to “create more room” for learning new tasks. The sole possibility of eliminating older mature neurons from the circuits and of replacing them with young neurons might be a key contribution of adult neurogenesis to hippocampal function (6).

For all three options discussed above, alteration of connections involving new neurons that are formed or modified by a learning experience should alter the animal’s memory of that experience (prediction IV).

**Experimental Evidence**

In most studies on adult neurogenesis, identification of newly generated neurons has been based on immunohistochemical data in which cells were simultaneously labeled for DNA replication and for the expression of specific neuronal proteins (10). Those experiments were carried out in fixed tissue and have rendered no functional data. To establish the physiological significance of neurogenesis in the adult brain, it is critical to demonstrate that newly generated neurons are true neurons that can shape brain function. At present, there is no evidence that expression of neuronal markers is related to neuronal function. The cell-biological question of neuronal function, a basic condition of the hypothesis, requires electrophysiology and/or imaging techniques to investigate whether cells that are born in the adult brain and express neuronal markers also display functional neuronal properties. Basic neuronal properties include excitability (spiking), functional synaptogenesis, and the capacity to synthesize and release neurotransmitters. More complex neuronal functions, such as integration of incoming signals, must also be analyzed, probably at a later stage. Finally, it will be necessary to show that alterations in neurogenesis may also modify behavior to determine its relevance for adult brain function.

The function of newly generated neurons in the adult hippocampus has been investigated at three levels: 1) the capacity of NPCs to generate functional neurons in culture; 2) the capacity of NPCs to produce functional neurons in vivo, through studies in brain slices; and 3) changes in neurogenesis being correlated with changes in behavior in animal studies.

**Functional neurogenesis in tissue culture**

It has been extensively shown that NPCs isolated from the adult brain of several species (including humans) can proliferate and differentiate into glia and neurons in culture (10, 17, 27, 34, 35). However, identification of neuronal phenotype in most of these studies has been based on morphology and expression of neuronal markers. A few reports have now demonstrated that progenitor cells from adult brain can display neuronal properties when differentiated under culture conditions. Voltage-dependent sodium currents were detected in cultured NPCs isolated from adult human hippocampus (34), suggesting that these cells might have the ability to spike. In addition, NPCs purified from the SVZ of adult rats displayed repetitive spiking in response to exogenous glutamate application (15). Definitive evidence of a functional neuronal phenotype came from studies carried out with progenitors isolated from adult rat hippocampus. When cultured in the presence of astrocytes, hippocampal NPCs produced neurons that generated action potentials, received functional GABAergic and glutamatergic synaptic inputs (45, 46), and could synthesize and release neurotransmitters (45). Interestingly, hippocampal astrocytes can promote neuronal differentiation and synaptogenesis of NPCs derived from adult hippocampus (44, 45), suggesting that they may play a critical role in functional neurogenesis. These observations suggest that NPC-glia interactions might contribute to the neurogenic properties encountered at the SGZ. Together, these observations demonstrate that, under specific culture conditions, NPCs from the adult brain can produce functional neurons.

A recent cell culture study has shown that depolarization-mediated calcium influx enhances neuronal differentiation of NPCs, indicating that neurogenesis may be highly influenced not only by the microenvironment provided by extracellular matrix components, cellular neighbors, and secreted factors but also by the activity of nearby neurons (7). These observations hint at the interesting possibility that hippocampal activity may be an important regulator of adult neurogenesis, in agreement with the finding that hippocampal neurogenesis is enhanced in animal models of epilepsy (28–30).

**Functional neurogenesis in live brain tissue**

The first and most compelling evidence that newly generated neurons are functionally incorporated into the existing circuits came from the remarkable work by Patton and Nottebohm in adult canaries (31). They labeled proliferating cells with [3H]thymidine and carried out blind electrophysiological recordings in the nucleus hyperstriatum ventralis pars caudalis (which is involved in vocal control) of live animals, using auditory stimuli to evoke synaptic responses. Recorded cells were identified as neurons by the presence of action potentials and were filled with horseradish...
peroxidase for immunochemical identification in fixed tissue. They observed that some neurons that had responded to auditory stimuli were double labeled for horseradish peroxidase and \(^{3}H\)thymidine, enough to demonstrate indisputably that they had recorded from newly generated neurons.

Intracellular recordings in mammalian brain slices have been limited by the difficulty imposed by identifying newborn cells in live tissue. Several approaches have been applied to overcome this caveat, including retroviral vectors encoding fluorescent proteins to label proliferating cells. In this way, adult-born cells can be identified by their fluorescence in live brain slices, and their electrophysiological properties can be monitored by applying the patch-clamp technique. This approach has proven successful in demonstrating that neurons generated in the hippocampus of young adult mice can spike and receive functional synaptic inputs from the entorhinal cortex, similar to mature DGCs (52). The presence of green fluorescent protein (GFP) in the soma and processes also allowed researchers to perform morphological analyses, which showed that newly generated neurons mature over a period of >4 mo. In this time, there was a significant increase in the complexity of the dendritic tree as well as in the density of dendritic spines. From these observations it was concluded that newly generated neurons are functionally integrated in the existing hippocampal circuits and that they can survive and mature over the course of several months. It is therefore very likely that they are relevant for hippocampal function. In fact, a recent study has shown that, compared with mature neurons, immature DGCs of the adult rat display a lower threshold for the induction of LTP in response to theta-burst stimulation of medial perforant-path afferents (39). This higher sensitivity for LTP induction suggests a relevant contribution of new neurons to adult hippocampal function, directly linked to the SPM hypothesis. Whether this higher level of plasticity is unique to immature DGCs or these properties remain after they reach functional maturation remains to be elucidated.

None of the studies described above have addressed whether new neurons can synthesize and release glutamate or to what extent their output properties may differ from those of mature DGCs (31, 39, 52). This information is particularly important considering that a small subpopulation of DGCs can release GABA (53), and it would be tempting to speculate that those GABAergic DGCs might originate during adulthood. Liu and collaborators (16) have recently demonstrated that the adult DG can generate not only functional DGCs but also GABAergic interneurons. Applying a combination of viral expression of GFP and bromoxygenuridine (BrdU) labeling, they carried out whole cell recordings from 169 pairs of cells in the DG and found 16 interneurons (probably Basket cells) that released GABA onto DGCs and were labeled with BrdU. Newly generated GABAergic interneurons also received functional afferents from the perforant path, demonstrating once more that new neurons are fully functional. Additional indirect evidence for functional neurogenesis was provided by labeling newly generated neurons in the DG with BrdU and a transsynaptic neuronal tracer (3) or colabeling with BrdU, neuronal markers, and immediate early genes used as indicators of neuronal activity (14). Therefore, there is little doubt that the adult hippocampus produces functional neurons. The challenge now will be to determine their precise role in hippocampal function.

Neurogenesis in the hippocampus has also been studied in animal models of brain pathology. In models of epilepsy, systemic administration of kainic acid or pilocarpine in adult rats induces spontaneous limbic seizures that, in turn, can cause an aberrant reorganization of mossy fiber synapses (24). Epileptic seizures greatly increase neurogenesis in the adult DG; the distribution of new neurons is not restricted to the granule cell layer; rather they also migrate ectopically to abnormal regions such as the dentate hilus (30, 37). It has been proposed that these ectopic neurons might play a key role in the pathogenesis of epilepsy. Ectopic neurons at the hilar-CA3 border can be readily recognized by their morphology and electrical properties (37), i.e., they do not require additional labeling to be identified in live tissue (although a small population of ectopic hilar granule cells present in control animals may complicate such identification (38)). Intracellular recordings carried out under these conditions showed that putative new neurons respond to stimulation of the perforant path, an additional piece of evidence for functional integration of newly generated neurons (38). However, whether these cells are physiologically relevant in the genesis of epileptic seizures remains unknown (29).

Some pathological conditions may induce functional neurogenesis in otherwise nonneurogenic regions of the hippocampus. A specific type of transient forebrain ischemia that causes a selective and massive degeneration of CA1 pyramidal neurons in the dorsal hippocampus of adult rats has also been shown to promote neurogenesis (25). In this model, intraventricular infusion of epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) induced a striking recovery in the number of CA1 pyramidal neurons and in the responsiveness to Schaffer-collateral stimulation, as a consequence of the differentiation of NPCs that proliferate and migrate from the periventricular area.
Recovery of neuronal function was accompanied by improved performance in the Morris water maze (25). This strong correlation between neurogenesis, recovery of synaptic function, and learning strongly supports the hypothesis requirement that new neurons must integrate into the existing circuits. However, here new neurons induce the recovery of lost function and do not seem to be participating in a specific mechanism of plasticity, such as the one proposed for the DG.

The observation that adult-born neurons are functional has not been restricted to hippocampal neurogenesis. Extensive evidence supports a physiological role for adult neurogenesis in the OB, although electrophysiological studies are scarce. The first direct evidence of functional integration of newly generated granule cells in the OB came from a study that used retroviral infection to express GFP in NPCs from the SVZ of adult mice to investigate the maturation of electrophysiological properties of migrating neuroblasts and mature neurons (4). This work showed that neurotransmitter receptors are expressed at early stages of neuronal development as neuroblasts migrate through the rostral migratory stream to the OB. Spontaneous synaptic transmission first appears during radial migration within the OB, before the onset of membrane excitability. New neurons receive GABAergic inputs first and glutamatergic transmission emerges later, a sequence that is similar to that reported for the development of CA1 pyramidal neurons (48). A more recent study has shown that newly born periglomerular cells display synaptic responses and, in some cases, action potentials in response to olfactory nerve stimulation, indicating that new cells have actually been incorporated into the existing olfactory circuits (2). Whether newly generated cells are GABAergic remains to be elucidated.

The evidence discussed above partially addresses requirement 1 of the hypothesis, that newly generated neurons are functional. It also suggests that new neurons might increase synaptic plasticity of the existing circuits, as shown by the lower threshold for LTP (39). To propose a solid model for the physiological role of new neurons in hippocampal circuits, it is still necessary to analyze their functional similarity with mature neurons in regard to intrinsic properties, neurotransmitter phenotype, axonal projections, and plasticity of synaptic inputs and outputs. It is also critical to establish whether those unique properties (such as lower LTP threshold) are long lasting or whether they are only expressed at particular stages of neuronal maturation.

**Behavioral studies**

The hypothesis proposed here states that neurogenesis is necessary for learning, but whether learning would alter neurogenesis is unclear. Should this be the case, learning would not be controlling the production of the very neurons that participate in that particular learning event. It is becoming clear that the making of a DGC with mature characteristics takes ~3–4 wk in the adult hippocampus and that new neurons can survive for several months (41, 52). The fact that neurogenesis is such a long-lasting process is not unique to the hippocampus, because similar data have been observed for the OB (4, 32). Therefore, a learning process that takes anywhere from seconds (such as in a passive-aversive paradigm) to days (such as the Morris water maze) has to make use of neurons generated a few weeks earlier that should be ready to connect within the existing circuits during the learning process. Thus a basal level of ongoing neurogenesis might be sufficient, so that new neurons would be available at all times to become incorporated in the circuit during learning. In this context, why would learning regulate neurogenesis? One possibility is that recruitment of new neurons would accelerate neurogenesis to replace the pool of cells that are being used up. Neurogenesis would proceed at a certain rate until usage of new neurons is increased, then this rate would be enhanced accordingly. Alternatively, learning could accelerate the death of older neurons and this, in turn, might increase neurogenesis (20, 25). Hence, it is likely that regulation of neurogenesis by a learning event would not modify the performance of the animal during that particular learning event, but it might be crucial for maintaining the level of hippocampal plasticity required for future tasks.

**Actions of learning and behavior on neurogenesis**

Regulation of neurogenesis by environment and behavior has been extensively reviewed (51). One of the first studies that hinted about a role for adult neurogenesis in hippocampal physiology and function showed that mice housed with a running wheel, a treatment that increases neurogenesis in the DG, displayed improved learning in the Morris water maze and enhanced LTP at perforant path-DGC synapses (49). This strong correlation between neurogenesis, learning, and LTP suggested that improved learning might be a consequence of increased plasticity, which, in turn, could be due to the contribution of synapses formed by perforant axons contacting dendrites of newly generated neurons. In agreement with this idea, the threshold for LTP induction at perforant path-DGCs is lower for immature neurons in the adult rat hippocampus, and an increase in the number of new DGCs might cause the
enhancement in LTP (39). In addition, the notion that a higher level of synaptic plasticity is directly associated with improved learning is now supported by growing evidence using genetic and pharmacological tools, in which manipulations that alter plasticity in a reversible manner also affect hippocampus-dependent learning accordingly (21, 22, 47). On the other hand, it is still possible that independent mechanisms are responsible for the increase in neurogenesis, LTP, and learning in running mice. To establish whether increased neurogenesis may enhance LTP and improve learning, it will be necessary to use genetic manipulations to selectively eliminate adult neurogenesis or new neurons in the adult hippocampus and then study the effects on synaptic plasticity and learning.

The effect of learning behaviors on the rate of cell proliferation, differentiation, and survival in the adult DG has also been examined. One study reported that successful training in hippocampus-dependent learning tasks increases the number of BrdU-positive cells in the adult rat DG (12). Both trace eye-blink conditioning and spatial navigation in the Morris water maze evoked a similar increase in cell proliferation and/or survival in the DG, suggesting a direct control of learning over neurogenesis (12). However, others have failed to find changes in cell proliferation, survival, or neuronal differentiation in adult mice DG after training in the Morris water maze (50). This apparent controversy could be due to differences in species, BrdU administration, or training protocols, but it suggests that regulation of neurogenesis by learning may be subtle or perhaps highly sensitive to the experimental conditions.

**Actions of neurogenesis in learning and behavior**

**Prediction 1** of the proposed hypothesis states that, if neurogenesis is required for learning, blockade of neurogenesis should impair memory formation. The time course of neuron generation and functional integration will be critical for testing the hypothesis. If new neurons were required for learning, how old should they be at the time of training? Ideally, neurogenesis should be abolished for a long enough interval so that all new cells that would have become functionally integrated before or during training could be eliminated. At present, the length of this time window remains uncertain. Immature neurons might be functionally integrated in the circuits 1–3 wk after mitosis (39), although more mature neurons seem to arise only after 4 wk (41, 52).

Adult neurogenesis has been prevented by using inhibitors of cell proliferation or X-ray irradiation. Both manipulations block cell proliferation in a nonspecific manner (not restricted to NPCs), and high doses may induce adverse secondary effects. For example, cranial irradiation, a method commonly used to abolish neurogenesis by killing proliferating NPCs, also induces inflammation that, by itself, decreases neurogenesis (23); inhibitors of cell proliferation can provoke weight loss and decline in overall health (42). Consequently, interpretation of those experiments should be cautious. Chronic treatment with methylazoxymethanol (MAM), a DNA-methylating agent that blocks cell proliferation, was reported to affect some forms of hippocampus-dependent learning (42). Systemic injection of MAM for 2 wk impaired eye-blink conditioning performance and decreased adult hippocampal neurogenesis, suggesting that decreased neurogenesis might have caused the impairment in memory formation (42). Although the impact on learning was significant, the effect of a 2-wk MAM treatment on the generation of functional neurons might have been partial, restricted to immature neurons. In fact, a MAM treatment carried out under a similar scheme did not alter performance in the Morris water maze (43), a result consistent with the notion that adult neurogenesis is not required for this form of hippocampus-dependent memory or, alternatively, that the selected treatment was not sufficient to fully block functional neurogenesis.

Additional experimental evidence in which adult neurogenesis is abolished by irradiation supports its key role in hippocampal function (19, 29, 36). Blockade of cell proliferation in the hippocampus by X-ray irradiation impairs performance in a T maze, a hippocampus-dependent learning task (39). Interestingly, although impairment was noticeable 2 wk after the onset of irradiation, the most prominent difference was found after 4 wk, a time point coincident with the expected maturational time for new neurons. In addition, a recent report demonstrates a key role of adult hippocampal neurogenesis in the effects of antidepressants in anxiety-related behaviors (36). This provocative work shows that chronic (4-wk) blockade of serotonin reuptake increases hippocampal neurogenesis and also reduces the latency in a novelty-suppressed feeding test. It is proposed that this reduction in latency, associated with reduced anxiety, is due to increased neurogenesis. The causal link between increased neurogenesis and the behavioral effect was investigated by abolishing neurogenesis by X-irradiation that, in turn, suppressed the behavioral effects of antidepressants. If the relationship were simply linear (“more neurogenesis brings less anxiety”), it would be expected that decreased neurogenesis should increase anxiety.
However, since irradiation did not affect latency in control mice, the connection seems to be more complex. It would be important to determine whether increased neurogenesis induced by other means (such as exercise, enriched environment, genetic manipulation) has similar effects on anxiety. It is also possible that, as proposed by the authors, the quality of the new neurons induced by antidepressants is different from that of basal neurogenesis. This evidence points to a role for adult neurogenesis in hippocampus-dependent behaviors that are not directly related to learning and memory. Therefore, a possible addition to the proposed hypothesis could be that neurogenesis is required for some specific behaviors that may or may not be related to learning and memory.

Concluding Remarks

Studies at the level of physiology, morphology, and behavior point to a role for neurogenesis in hippocampal function. Fundamental observations include the following: 1) NPCs generate functional neurons in vitro and in vivo in the appropriate neurogenic environments; 2) differentiated neurons become integrated in the existing networks; 3) these neurons grow and establish new connections for long periods of time (i.e., months); 4) immature neurons have increased synaptic plasticity; and 5) certain manipulations that affect hippocampal neurogenesis can modify hippocampus-dependent behaviors, including some forms of learning.

However, current data are insufficient to establish the precise physiological role of new neurons and to determine to what extent this role is related to the synaptic plasticity and memory hypothesis. Moreover, the nature of learning and behaviors that require neurogenesis remain unclear. In this regard, the most important limitation arises from the difficulty to manipulate the levels of neurogenesis at the right time and in the right place, so that behavioral consequences will be fully manifested at the time of experimental observation. This problem calls for genetic models in which neurogenesis in the DG can be switched on and off during adulthood, where learning and memory can be studied in depth in mice lacking adult hippocampal neurogenesis.

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