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Is There A Link Between Adult Neurogenesis and Learning?

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ABSTRACT: During the past several years, evidence has accumulated suggesting a relationship between newly born cells in the hippocampus and various types of learning and memory. However, most of the evidence is correlational and some of it does not agree. This review discusses both sides of this issue, considering the effects of learning on the production of new neurons in the dentate gyrus and the question of whether newly born cells participate in learning and memory. © 2006 Wiley-Liss Inc.

KEY WORDS: dentate gyrus; water maze; hippocampus; memory; BrdU; eyeblink conditioning

INTRODUCTION

The involvement of the hippocampus in learning and memory has long been recognized (Scoville and Milner, 1957; Squire, 1982; Moscovitch et al., 2005). It is usually assumed that synaptic plasticity within the hippocampal formation contributes to the acquisition and retention of memories (Martin et al., 2000; Lamprecht and LeDoux, 2004) but the exact mechanisms remain unknown. Over the past 40 years, a considerable body of evidence has accumulated indicating that the dentate gyrus (DG) of the adult hippocampus produces new neurons in substantial numbers and does so in a wide range of mammalian species, including humans (Altman and Das, 1965; Kaplan and Hinds, 1977; Cameron et al., 1993; Kempermann et al., 1997; Eriksson et al., 1998: Gould et al., 1998, 1999a). Collectively, these observations have led to the hypothesis that adult neurogenesis participates in hippocampal functions, especially those related to learning and memory (Barnea and Nottebohm, 1994; Gould et al., 1999b; Gross, 2000; Kempermann, 2002). This idea, only recently tested, is not without precedent.

Altman and colleagues may have been the first to suggest a role for postnatally generated cells in learning (Bayer et al., 1973; Gazzara and Altman, 1981). However, the idea that adult-generated neurons were involved in learning was discussed and studied first by Nottebohm and coworkers in relation to song learning in birds (Goldman and Nottebohm, 1983; Nottebohm, 1985). Subsequent work considering seed caching behavior and the avian homolog of the hippocampus led to the extension of the idea that adult neurogenesis is important for learning and memory of spatial information (Barnea and Nottebohm, 1994, 1996). The potential relevance of these findings to learning in mammals was not generally accepted until it became clear that new neurons in the DG become synaptically integrated (Hastings and Gould, 1999; Markakis and Gage, 1999; Carlen et al., 2002), attain morphological and biochemical characteristics of neurons (Cameron et al., 1993; Kuhn et al., 1996) and generate action potentials (van Praag et al., 2002). Although interest in adult neurogenesis has grown exponentially in recent years, evidence for a role of adult-generated granule cells in learning and memory remains limited and in most cases indirect. In this review, we consider possible evidence in favor of and possible evidence against a role for adult neurogenesis in learning. The available evidence is presented in three experimental categories: 1. studies that correlate the number of new neurons with learning abilities; 2. studies that examine the influence of learning on the number of new neurons that are produced and/or survive; and 3. the effects of new neuron depletion on learning and memory.

IS THE NUMBER OF NEW NEURONS POSITIVELY CORRELATED WITH LEARNING?

Several factors and conditions have been shown to affect the number of new neurons in the dentate gyrus (DG) of adult vertebrates (see other reviews in this issue). Many of these have also been shown to influence certain types of learning and memory. Positive correlations between the number of new neurons and learning performance would imply a relationship between neurogenesis and learning, although not necessarily a causal one. There are a number of other issues that should be kept in mind when evaluating these data. For instance, much of the available evidence comes from separate sets of experiments—those that have examined the effects of a certain factor on neurogenesis and those that have examined the effects of that same factor on performance during learning tasks. Because most of these data were acquired from different sets of animals, statistical correlations between learning and neurogenesis cannot be obtained. Another consideration is that the time course for alterations in cell production may not necessarily correspond to changes in learning abilities. For example, it seems unlikely that the production of new cells would have an immediate effect on processes involved in learning because the cells require time to differentiate into neurons and become integrated

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into the existing circuitry (Cameron et al., 1993; Hastings and Gould, 1999; Markakis and Gage, 1999; Carlen et al., 2002; van Praag et al., 2002). Perhaps an even more important consideration, and one that is impossible to discount, is the fact that many of the factors known to affect neurogenesis also alter other aspects of brain structure and function, such as dendritic architecture, synapse number, and synaptic plasticity. Since these types of changes are also likely to be involved in hippocampal-dependent learning, it is difficult to interpret correlations between new neurons and learning. With these caveats in mind, there are a number of studies that report positive correlations between neurogenesis and learning, as well as a number that have found no correlation or even a negative one.

Evidence in Favor

Studies in birds were the first to provide evidence for a positive relationship between adult neurogenesis and learning. In the song system of canaries, the production of new neurons occurs in the high vocal center (HVC) and is positively related to sex and seasonal differences in song learning (Goldman and Nottebohm, 1983; Alvarez-Buylla et al., 1990). Likewise, in the hippocampal region of black-capped chickadees, a seasonal fluctuation in adult neurogenesis is positively related to engaging in spatial learning behaviors, namely seed storage and retrieval (Barnea and Nottebohm, 1994).

Several lines of evidence also suggest a correlation between adult neurogenesis and learning in mammals. Strain differences in the rate of adult neurogenesis in mice have been shown to parallel strain differences in learning. That is, the mice with the fewest number of new neurons performed most poorly during spatial navigation learning in the Morris water maze task (Kempermann and Gage, 2002). In rats, numerous conditions that decrease adult neurogenesis in the DG are associated with learning impairments. These include, but are not limited to, stress (reviewed by Mirescu and Gould, this issue), increased levels of circulating corticosteroids (reviewed by Mirescu and Gould, this issue), and aging (Kuhn et al., 1996; Bizon and Gallagher, 2003; Drapeau et al., 2003). In one study (Drapeau et al., 2003), the number of new cells in aged rats and performance during spatial navigation learning was assessed in the same animals and a positive statistical correlation between the two measures was found. Separate studies have also shown that stress and elevated glucocorticoids are associated with decreased production of new cells (Gould et al., 1998; Tanapat et al., 2001) and impaired learning on hippocampal-dependent tasks (Luine et al., 1994; de Quervain et al., 1998; Diamond et al., 1999). Similarly, adverse prenatal or early life experiences produce persistent reductions in neurogenesis (Lemaire et al., 2000; Mirescu et al., 2004) and reduced learning abilities in adulthood (Lemaire et al., 2000; Huot et al., 2002). There are also a number of drugs that are associated with decreases in neurogenesis, such as alcohol, nicotine and opiates (Eisch et al., 2000; Abrous et al., 2002; Nixon and Crews, 2002), all of which can, in the appropriate doses, result in performance deficits during some learning tasks (Spain and Newsom, 1991; Matthews and Silvers, 2004; Scerri et al., 2005). Again, it is noted that although many studies suggest that decreasing neurogenesis is associated with impaired learning, most of these studies cannot provide statistical correlations.

Conditions that increase the number of immature neurons such as estrogen (Tanapat et al., 1999), environmental complexity (Kempermann et al., 1997), and physical exercise (van Praag et al., 1999) also tend to enhance performance on hippocampal-dependent learning tasks (Daniel et al., 1994; Kempermann et al., 1997; Luine et al., 1998; van Praag et al., 1999; Leuner et al., 2004a). Although statistical correlations are not available, it has been reported that environmental complexity and physical exercise enhance neurogenesis and learning in the same animals (Kempermann et al., 1997; van Praag et al., 1999).

Evidence Against

Despite these studies suggesting a positive correlation between neurogenesis and learning, there are a number of reports in which this relationship has been dissociated or appears to be reversed. For example, unlike in mice, strain-dependent differences in hippocampal neurogenesis do not correlate with spatial navigation learning in rats (Van der Borght et al., 2005a). Moreover, although conditions of elevated glucocorticoids such as stress and aging diminish cell proliferation in the DG, they do not necessarily result in learning deficits on hippocampal-dependent tasks (Bizon and Gallagher, 2003; Akirav et al., 2004). In fact, stressor exposure has been shown to enhance learning of certain hippocampal-dependent memory tasks (Wood et al., 2001; Leuner et al., 2004b), which may suggest an inverse relationship between the number of new neurons and learning. Indeed, an inverse relationship between hippocampal neurogenesis and learning has been reported in the tree shrew; chronic stress diminishes the production of new neurons but appears to improve performance on a spatial navigation task (Bartolomucci et al., 2002). Similarly, although positive regulators of adult neurogenesis, such as estrogen, have been associated with enhancements in learning (Daniel et al., 1994; Luine et al., 1998; Leuner et al., 2004a), learning deficits have also been reported (Holmes et al., 2002).

In summary, the available evidence concerning potential correlations between learning and neurogenesis is incomplete and mixed. As an alternative to the correlational approach, a number of studies have addressed the potential connection between adult neurogenesis and learning by examining the influence of learning itself on the number of adult-generated cells. Next, we review the studies that have used such an approach.

DOES LEARNING INCREASE THE NUMBER OF NEW NEURONS?

During development, activity in neural circuits stabilizes and sustains those circuits into adulthood (Katz and Shatz, 1996; Ben-Ari, 2001). Thus, it seems plausible that activation of new neurons would enhance the production and/or survival of those

cells. The studies discussed in this section all involve attempts to explore the effects of various learning tasks on the number of new cells that are produced and/or survive. As with the correlational data presented above, the findings are mixed.

Evidence in Favor

Training on learning tasks that require the hippocampus has been shown to alter the numbers of new neurons in the DG. However, the direction of the effect is not always the same. For example, it has been shown that training with trace eyeblink conditioning, spatial learning in the Morris water maze and conditioned food preference increase the number of newborn cells in the DG of adult rats (Gould et al., 1999c; Ambrogini et al., 2000; Lemaire et al., 2000; Dobrossy et al., 2003; Leuner et al., 2004c; Hairston et al., 2005; Olariu et al., 2005). These effects appear to be specific to learning that requires the hippocampus. Some studies have shown that learning tasks that do not require the hippocampus, but which nonetheless activate or engage it (e.g., delay eyeblink conditioning, cue–maze training, active shock avoidance) (Weisz et al., 1984; Ramirez and Carrer, 1989; Shapiro et al., 1997), do not change the number of new granule neurons in the DG of the hippocampus (Gould et al., 1999c; Van der Borght et al., 2005b).

Evidence Against

In contrast to the studies demonstrating a stimulatory effect of learning on adult neurogenesis, there are also reports that training on various learning tasks either does not alter the number of new neurons in the hippocampus (van Praag et al., 1999; Snyder et al., 2005; Van der Borght et al., 2005a) or actually decreases it (Dobrossy et al., 2003; Ambrogini et al., 2004a; Olairu et al., 2005; Pham et al., 2005). There are several possible reasons for these discrepant findings.

One possibility is that the influence of learning on new neuron number depends on the age of the BrdU labeled cells at the time of learning. Trace eyeblink conditioning and water maze training enhance the survival of new cells born one week prior to training, when they are during early stages of differentiation and most susceptible to cell death (Gould et al., 1999c; Ambrogini et al., 2000). In contrast, learning appears to decrease the survival of older and perhaps more mature newborn neurons (Ambrogini et al., 2004a). Thus, certain BrdU labeling paradigms may not be appropriate for detecting increases in new cell number with learning. Indeed, if learning both increases and decreases in the number of new neurons, depending on the age of the cells at the time of training, then BrdU labeling, which occurs over many days, may result in an overall lack of a difference in the number of labeled cells. For example, a recent study reported an increase in the number of cells that stain for PSA-NCAM, a marker of immature neurons in the DG, in response to training on the Morris water maze with no corresponding change in the number of BrdU-labeled cells (Van der Borght et al., 2005a). Although the authors concluded that they found no increase in adult neurogenesis with learning, an alternative interpretation of these data is that learning did result in a net increase in new neurons, i.e., an increase in the number of PSA-NCAM positive cells, but that the BrdU injections (which occurred over 3 days) failed to reveal an increase because multiple processes were occurring at the time the cells were labeled.

Another possibility is that the varied effects of learning on adult neurogenesis may be the result of differences in the training protocols. Olariu et al. (2005) have shown that the amount or number of training trials that an animal is exposed to determines whether the effect on adult neurogenesis is positive or negative. Applying this interpretation to the larger literature on this subject, it seems that fewer training trials have been associated with enhanced cell survival whereas a greater number of trials have been associated with no effect or decreases in survival (Gould et al., 1999c; Dobrossy et al., 2003; Ambrogini et al., 2004a; Olariu et al., 2005; Snyder et al., 2005). However, this relationship does not extend itself to training with all types of tasks. With trace eyeblink conditioning, exposure to just 200 trials of training did not enhance cell survival, whereas training with 800 trials did (Leuner et al., 2004c). It is important to note that even though the overall number of newborn cells was not affected by a shorter training episode, the number of learned responses emitted during the 200 trials of training was positively correlated with the number of cells that survived. These data would suggest individual differences in early acquisition are predictive of whether new neurons will survive. Moreover, they are consistent with recent findings that suggest that different phases of the learning process (i.e., acquisition, retention, retrieval) must be taken into account when assessing the effects of learning on adult neurogenesis (Kempermann and Gage, 2002; Dobrossy et al., 2003). Taken together, it is clear that more studies will be needed to resolve the question of whether learning alters the number of new neurons in the DG.

ARE NEW NEURONS NECESSARY FOR LEARNING?

Definitive evidence for a requirement of new neurons can only be obtained by demonstrating deficits in hippocampal function following selective depletion of new neurons. Designing experiments to address this question has been difficult for two major reasons. First, methods to selectively deplete new neurons without affecting other aspects of brain function are not yet available. To date, the published experiments have used either antimitotic drugs or irradiation to decrease adult neurogenesis. Both of these methods can induce nonspecific effects on performance or brain function raising the possibility of false positive results. Second, the timing and duration of neuron depletion may be a critical factor in detecting learning deficits. New neurons may participate in learning for only a discrete period after their production and detecting a learning deficit may require depletions of a certain length prior to behavioral assessment. False negative results could occur if neuron depletion is insufficient in length or the interval between depletion and training is inappropriate. False negative results could also

arise if neuron depletion occurs for too great a time period such that compensatory mechanisms come into play. Thus, ruling out a possible role for adult-generated neurons in any type of learning would require numerous schedules of neuron depletion along with assessing performance during different phases of the learning process. Finally, since the hippocampus has been linked to a number of different types of learning with no obvious common theme (e.g., trace eyeblink and fear conditioning, contextual fear conditioning, spatial navigation learning, delayed nonmatch to sample), detecting and characterizing a role for new neurons in learning will require extensive behavioral assessment. Notwithstanding these methodological considerations, several studies have attempted to answer the question of whether new neurons are used in the acquisition and/or retention of new memories.

Evidence in Favor

The antimitotic agent methylazomethanol acetate (MAM) has been used to block adult neurogenesis in rats (Shors et al., 2001). A substantial reduction in the number of adult born cells resulting from MAM treatment over a 2-week period was associated with an impaired ability to acquire the trace eyeblink conditioning task. Similar treatment in a separate group of animals was not associated with deficits during training on delay conditioning, using parameters that do not depend on the hippocampus. When the population of new neurons was allowed to replenish itself, the ability to acquire trace memories was restored. Similarly, a reduction in the number of new cells after MAM treatment was associated with deficits on a fear memory task (Shors et al., 2002), which depends on the hippocampus (McEchron et al., 1998).

Although these findings suggest a relationship between neurogenesis and learning, the studies themselves are not without their drawbacks. For one, there is the possibility that MAM has other effects on cellular plasticity or even general health, aside from those on neurogenesis, which are responsible for the learning deficits. In the studies mentioned earlier, there was an attempt to rule out the most obvious side effects such as overt changes in activity, anxiety, pain sensitivity, and measures of hippocampal plasticity such as long-term potentiation (LTP). However, it is impossible to rule out all possible effects. Thus, decreases in performance due to effects in other brain regions or other aspects of performance that can impinge on learning are conceivable. It has also been suggested that the learning deficits from MAM administration result from toxic effects of the drug. A recent study even suggested that "extreme caution" should be used when evaluating studies that have used MAM. In the study, MAM treatment was shown to induce weight loss and fur deterioration (Dupret et al., 2005), but only at the highest doses tested (10 mg/kg and 14 mg/kg), consistent with weight loss and health deterioration at higher doses described by Shors et al. (2001). However, the lower doses of MAM (5–7 mg/kg) used in studies showing learning impairments (Shors et al., 2001, 2002; Bruel-Jungerman et al., 2005) do not produce detectable weight loss or other health problems (Shors et al., 2001; Dupret et al., 2005). Nonetheless, it is still possible that undetectable yet detrimental effects of the drug on health or performance could contribute to the deficits in learning.

To circumvent some of the problems associated with systemic administration of cytostatic agents such as MAM, some studies have used localized irradiation to reduce the population of newly generated cells in the DG (Madsen et al., 2003; Raber et al., 2004; Rola et al., 2004; Snyder et al., 2005). Moreover, irradiation has the advantage over antimitotic agents in that the population of new cells is usually depleted completely rather than just reduced. With complete depletion, possible conclusions regarding the involvement of adult-generated neurons in learning become more convincing.

Irradiation was first used by Altman and colleagues to demonstrate the importance of early postnatal neurogenesis for certain types of learning in adulthood such as conditioned avoidance and discrimination learning (Bayer et al., 1973; Gazzara and Altman, 1981). However, since most granule cells are born during the early postnatal period, the irradiation procedure essentially lesioned the granule cell layer and thus a direct connection between neurogenesis and learning could not be made. More recently, this method has been applied to adult rats such that irradiation only reduces cell production in adulthood, presumably leaving the developmentally generated granule cells intact (reviewed by Wojtowicz, this issue). These studies have reported deficits in various types of hippocampal-dependent learning tasks. For example, the performance of irradiated rats was impaired on a hippocampal-dependent place recognition task, but not on an object recognition task, which is not dependent on the hippocampus (Madsen et al., 2003; Rola et al., 2004). However, like the antimitotic agents, there are some possible side effects of using irradiation to block adult neurogenesis, which could inadvertently affect performance. Most notably, irradiation can induce inflammatory responses, which can impact aspects of behavior and physiology that may in turn impact performance during learning tasks (Monje et al., 2002; Rola et al., 2004). Thus, the extent to which cognitive deficits following irradiation are attributable to a loss of newly born cells in the DG remains unknown.

Evidence Against

Despite the reports that depletion of new cells results in learning deficits, there are probably an equal number that have failed to demonstrate that newly generated cells are involved in hippocampal-dependent learning. As noted, exposure to the MAM treatment, which significantly reduced the population of new cells, did not result in a deficit in spatial navigation in the Morris water maze, nor was there any effect on the expression of contextual fear conditioning (Shors et al., 2001, 2002). Similarly, others have found no effect of irradiation-induced depletion on spatial learning in water maze task (Madsen et al., 2003; Raber et al., 2004; Snyder et al., 2005). One interpretation of these findings is that newly born cells are not required for these tasks. Alternatively, these learning

tasks may not be sufficiently sensitive to the loss of newly generated hippocampal neurons. Variations on hippocampal-learning tasks, which place greater demands on the cognitive abilities of the animals, may reveal deficits (Gazzara and Altman, 1981; Beylin et al., 2001; see Winocur, this issue). This possibility is supported by data demonstrating irradiation-induced deficits in other paradigms involving spatial processing, including the Barnes maze and place recognition (Rola et al., 2004). It has also been proposed that for some tasks only a limited number of cells may be needed to sustain performance (Shors et al., 2002; Dupret et al., 2005). Data showing that spatial navigation in the water maze is maintained in aged rats with very low numbers of newly born cells has been cited as support for this hypothesis (Bizon and Gallagher, 2003; Drapeau et al., 2003). As with the effects of learning on the number of new neurons, here too it may be important to distinguish among different phases of the learning process. A recent study suggests that while adult-generated cells may not be important for acquiring spatial information in the water maze, newly born cells are required for long-term spatial memories (Snyder et al., 2005).

HOW MIGHT NEW NEURONS PARTICIPATE IN LEARNING AND MEMORY?

Although new neurons are predicted by some computational theories of learning (Chambers et al., 2004; Diesseroth et al., 2004; Becker, 2005), their precise role is not yet known. It has been suggested that the production of new cells in the DG increases the opportunity for learning in the future by providing more cells that can be recruited into existing circuits (Kempermann, 2002). However, it is possible that newly born cells influence learning processes even before they achieve full maturation. Certain characteristics of synaptic plasticity are enhanced in adult-generated neurons and these characteristics may make them particularly useful for the processing of new associations. The induction threshold for LTP is lower for young granule cells in the DG and is also insensitive to GABAergic inhibition (Wang et al., 2000; Snyder et al., 2001; Ambrogini et al., 2004b; Schmidt-Hieber et al., 2004). Whether adult-generated cells retain these properties after they achieve maturity remains to be determined. Regardless, these unique properties of adult born, immature neurons may qualify them for functions that mature developmentally generated cells are less suited to accomplish (Gould et al., 1999b). For example, it has been suggested that new cells born in adulthood could be used to detect or process novel stimuli (Kempermann, 2002; Shors, 2004; Becker, 2005), a function that has been ascribed to the hippocampus (Lemaire et al., 1999; Nyberg, 2005).

Another possible role for new neurons in hippocampal function may be related to temporary storage of information (Gould et al., 1999b; Gross, 2000). It is generally believed that the hippocampus plays a time-limited role in memory storage. Support for this view derives from studies in which lesions to the hippocampus become less effective at disrupting task performance as more time elapses between acquisition and memory recall (Kim et al., 1995; Takehara et al., 2003; Moscovitch et al., 2005). The possibility that adult-generated cells participate in time-limited memory storage has been suggested for both memories of seed caching in black capped chickadees (Barnea and Nottebohm, 1994) as well as learning in canaries where the birth and death of HVC neurons parallels the seasonal modification of song (Kirn et al., 1994). The same possibility may apply to the mammalian hippocampus—a rapidly changing population of adult-generated neurons may provide a substrate for maintaining memories over relatively short periods of time (Gould et al., 1999b). Accordingly, one might predict that the lifespan of a new neuron would correspond to the duration of the memory that it supports. However, this is not necessarily the case. It has been reported that learning increases the survival of new neurons in the hippocampus and they remain there for at least two months after training (Leuner et al., 2004c), which is well beyond the time when the hippocampus is required for the retention of those memories (Kim et al., 1995; Takehara et al., 2003). These findings do not exclude the possibility that new neurons participate transiently in memory storage but rather, that if that is their role, eventually they may outlive their usefulness, perhaps becoming important for some other function.

FUTURE DIRECTIONS

To date, the amount of conclusive evidence linking adult neurogenesis and learning is small (Table 1). This limited understanding can be partially attributed to the fact that appropriate methods to manipulate and monitor new neuron production in adulthood do not exist. Thus, a critical direction for future research examining the role of adult-generated neurons in learning will be the development of new techniques such as transgenic mice in which new neuron production in the DG could be selectively and reversibly ablated. Beyond this, more refined molecular techniques could be used to detect changes in the new cells as the animal is engaged in a learning experience.

Even with these new technologies, a number of fundamental questions will remain. For example, what are the mechanisms by which cell production in the DG is regulated during learning? Do new neurons rescued by learning show different patterns of connectivity relative to other adult-generated neurons or those generated during development? Is gene expression in new neurons affected by learning and does it differ from that in mature neurons? At an information processing level, how does a new population of neurons interact with those neurons that were generated during development and how do these interactions lead to the formation of new memories without destroying old memories? Addressing most of these questions will require a better understanding of the functional maturation of adult-generated neurons (Carlen et al., 2002; Dayer et al., 2003; Ambrogini et al., 2004b) as well as insight into the dif-

TABLE 1.

Evidence in Favor of and Against a Role for Adult Neurogenesis in the Hippocampus in Learning and Memory

Is the number of new neurons positively correlated with learning?

Factor	Evidence in favor	Evidence against
Stress	Luine et al. (1994), Gould et al. (1998), Diamond et al. (1999), Tanapat et al. (2001)	Wood et al. (2001), Bartolomucci et al. (2002)
Glucocorticoids	de Quervain et al. (1998)	Akirav et al. (2004)
Aging	Kuhn et al. (1996), Drapeau et al. (2003)	Bizon and Gallagher (2003)
Estrogen	Daniel et al. (1994), Luine et al. (1998), Tanapat et al. (1999), Leuner et al. (2004a)	Holmes et al. (2002)
Enriched environment	Kempermann et al. (1997)	
Physical activity	van Praag et al. (1999)	
Adverse prenatal/early life experience	Lemaire et al. (2000), Huot et al. (2002), Mirescu et al. (2004)	

Does learning increase the number of new neurons?

Factor	Evidence in favor	Evidence against
Trace eyeblink conditioning	Gould et al. (1999c), Leuner et al. (2004c)	
Social transmission of food preference	Olariu et al. (2005)	Olariu et al. (2005)
Spatial water maze	Gould et al. (1999c), Ambrogini et al. (2000), Dobrossy et al. (2003), Hairston et al. (2005)	van Praag et al. (1999), Dobrossy et al. (2003), Ambrogini et al. (2004a), Snyder et al. (2005), Van der Borght et al. (2005a)

Are new neurons necessary for learning?

Factor	Evidence in favor	Evidence against
Trace eyeblink/fear conditioning	Shors et al. (2001), Shors et al. (2002)	
Contextual fear conditioning	Winocur et al., this issue	Shors et al. (2002)
Delayed nonmatch to sample	Winocur et al., this issue	
Spatial learning		
Water maze		Shors et al. (2002), Madsen et al. (2003), Raber et al. (2004), Snyder et al. (2005)
Place recognition	Madsen et al. (2003), Rola et al. (2004)	
Barnes maze	Rola et al. (2004)	
Spatial memory	Snyder et al. (2005)	

ferences and similarities between neurons generated during development vs. those produced in adulthood. Until now, addressing such issues has been inhibited by technical limitations but may be more feasible given a number of recent advances. It is now possible to use dual cell cycle labels with markers of cell phenotype (Vega and Peterson, 2005). This method could allow for not only the comparison of developmentally and adult-generated neurons in the same animal, but also how these different cell populations are affected by learning. Addressing differences in gene expression in adult-born neurons can be achieved with laser capture microdissection (LCM). LCM has recently been used to demonstrate differential gene expression in replaceable vs. nonreplaceable populations of neurons in birds and mice (Lombardino et al., 2005). Combining LCM with immunocytochemistry could then be used to show how learning alters gene expression within the new neuron itself.

Clearly, a definitive link between adult neurogenesis in the hippocampus and learning remains to be established. Whether or not a role for adult-generated neurons in learning and memory is ultimately ruled out, alternative functions should be considered. One possibility is that adult neurogenesis is a vestige of development, which, in adulthood, has no functional significance. However, given the substantial number of new neurons that are produced in the hippocampus in adulthood (Cameron and McKay, 2001; Dayer et al., 2003), even in humans (Eriksson et al., 1998), it is unlikely that these cells serve no function. Alternatively, new neurons may contribute to other functions of the hippocampus, such as anxiety and stress regulation, or they may serve as a latent mechanism for endogenous repair

of this brain region, known for its susceptibility to ischemia and seizures. Now that a critical mass of neuroscientists are turning their attention to the questions of adult neurogenesis with open minds, definitive answers will undoubtedly emerge.

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