Adult neurogenesis: a substrate for experience-dependent change

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A rapidly growing body of literature indicates that adult neurogenesis in the hippocampus is sensitive to a variety of environmental factors. The effects of emotionally salient experiences, such as stress and physical exercise, have been characterized extensively with regard to both adult neurogenesis and behaviors associated with the hippocampus. Experience-dependent changes in the production and function of new neurons may serve as a means to fine-tune the hippocampus to the predicted environment. Here, we discuss this possibility along with the argument that more naturalistic experimental conditions may be a necessary step toward understanding the adaptive significance of neurons born in the adult brain.

Shaping the adult brain through experience

More than 100 years ago, Santiago Ramon y Cajal wrote, 'Any man could, if he were so inclined, be the sculptor of his own brain.' [1] This statement was amazingly prescient, given how little was known at the time about the plasticity inherent to the adult brain. After a virtual explosion in research focused on neural plasticity in recent years, it has become increasingly clear that environmental influences, including specific experiences, have a profound effect on adult brain structure and function [2]. Much attention has focused on the hippocampus in this regard, both because of its role in important functions, such as certain types of learning and memory, and its impressive degree of structural plasticity. The hippocampus displays a high rate of adult neurogenesis, specifically within the dentate gyrus where new granule cells (see Glossary) are produced throughout life [3]. Adult neurogenesis in the dentate gyrus has been demonstrated in a range of mammalian species, including humans [3,4], and the process of adult neurogenesis has been shown to be strongly influenced by the environment [2,5]. Evidence suggests that experience-dependent changes in adult neurogenesis are associated with major changes in hippocampal function, both for better and for worse. The relation between experience and functional neurogenesis has been studied extensively, but questions remain with respect to how refinements in neuron numbers integrate with other types of structural change to produce large-scale behavioral modifications.

Identification of experiences that alter adult neurogenesis in the hippocampus may provide clues to the functional significance of new neurons. Findings from the overall literature on experiential modulation of adult neurogenesis seem to converge on a basic model: aversive experiences, such as social defeat or predator odor exposure, tend to decrease the production of new neurons, whereas more rewarding experiences, such as physical activity or mating, tend to increase the production of new neurons [2,5]. Taken together with results demonstrating a role for adult neurogenesis in hippocampal function, this model suggests that new neurons serve as a substrate by which experience can shape the hippocampus so that it is fine-tuned to the environment. However, to reach this conclusion, a clear understanding of how experience regulates adult neurogenesis, as well as the known behaviors linked to new neurons, is necessary. A vast literature has explored the influence of various experiences on adult neurogenesis (Figure 1); of these studies, most have focused on two types of experience, namely, stress and physical activity, each producing generally opposite effects on the number of new neurons.

Stress effects on adult neurogenesis and hippocampal function

Stressful experiences, such as restraint, social defeat, predator odor exposure, inescapable foot shock, sleep deprivation, as well as a regimen of different stressors combined, have been shown to decrease the number of new neurons in the dentate gyrus [2,5–9]. Although a few studies have reported enhanced adult neurogenesis with certain stress paradigms [10,11], the stressors in these cases were predictable, mild, and may have added enriching complexity to an environment, an experience known to

Glossary

Cytokines: molecules that are released by immune cells, including microglia.
Dentate gyrus: subregion of the hippocampus that is a major site of adult neurogenesis.
Glucocorticoids: steroid hormones that are released by the adrenal gland in response to stress.
Granule cells: the main excitatory neurons of the dentate gyrus.
Hypothalamic–pituitary–adrenal axis: stress system that includes the hypothalamus, pituitary, and adrenal gland that work together to control levels of circulating glucocorticoids.
Microglia: a type of glia that responds to disease and damage by becoming activated and helping to clear debris.
Oligodendrocytes: a type of glia that makes myelin, a substance that wraps around and insulates axons.
Progenitor cells: stem-like cells that divide and produce new cells, including neurons.

enhance adult neurogenesis (Figure 1). However, when the stressor is unpredictable and relatively intense, the effect on adult neurogenesis is typically negative.

The literature on this topic is large, with studies indicating multiple stages in the adult neurogenesis process during which stress has an inhibitory effect. First, stress has been shown to suppress the proliferation of progenitor cells that produce new neurons. This effect has been demonstrated in a range of mammalian species, including rats, mice, marmosets, and macaques [5,7,11]. Not only does stress result in a net decrease in the number of proliferating cells, but some evidence also suggests that stress shifts neural stem cells in the hippocampus away from the production of neurons and toward the generation of oligodendrocytes [12]. It is not clear how a combined decrease in new neurons and increase in new oligodendrocytes affects hippocampal function, but the latter effect may alter myelination of axons coursing through the dentate gyrus. However, it remains unknown whether new oligodendrocytes would contribute to myelination of axons of new neurons, which are generally known to be unmyelinated [13]. It is additionally unknown whether the effects of stress on new neurons and oligodendrocytes would follow similar or different time courses. Second, stress has been shown to delay neuronal differentiation, that is, the maturation of a cell into a neuron [5,7,11]. Third, stress reduces the survival of neurons produced before the stressful experience. Although the mechanism that underlies this effect remains unknown, stress is known to reduce expression of brain-derived neurotrophic factor (BdNF), a molecule known to enhance cell survival [11]. A reduction in the survival of new neurons is also likely to engage another population of nonneuronal cells, the microglia, which are known to engulf new neurons in the dentate gyrus. Stress

has been shown to have a profound effect on the number of microglia, as well as their state of damage-induced reaction [6]. Although stress-induced reaction of microglia may be important for cleaning up the debris left behind by dead new neurons, it remains possible that microglia play an active role in reducing new neuron survival, either by releasing cytokines with neurotoxic effects, or by actively engulfing new neurons before their definitive demise (Box 1).

Evidence suggests that elevated levels of glucocorticoids are, at least in part, responsible for the effects of stress on new neuron production [5]. Exogenous glucocorticoid administration has similar effects as stress on cell proliferation, neuronal differentiation, and cell survival, as well as on oligodendrocyte production and microglial reaction [6,12]. Furthermore, some evidence suggests that stress effects on new neuron production can be prevented by interfering with stress-induced increases in glucocorticoid levels [5].

Stress-induced suppression of adult neurogenesis has been associated with impaired performance on cognitive tasks that require the hippocampus, such as spatial navigation learning and object memory [5,14–16]. It should be noted that stress has been shown to facilitate certain types of learning, but these effects are typically observed within a shorter time frame than what would be expected for the involvement of new neurons [17]. Stressful experiences have also been shown to increase anxiety-like behaviors that are associated with the hippocampus, including those measured with the elevated plus maze, open field, and novelty suppressed feeding tasks [5,11] (Figure 1). The extent to which these behavioral changes are directly linked to reduced numbers of new neurons remains unknown [5] (Box 2), but data from studies examining other

	Stimulus	Adult neurogenesis	Cognitive performance	Anxiety-like behavior	References
Negative	Stress				5,8,82,83
Negative	High fat diet/obesity				84,85
Positive	Physical exercise				18,19,21,22,39
Positive	Sexual experience				36,86,87
Positive	Enriched environment (EE)				89,90
Positive	Intracranial self-stimulation				91,92
Mixed	Parenting				34,35,88,93
Mixed	Stress + physical exercise				74,75,94
Mixed	Stress + sexual experience				76,95
Mixed	Stress + EE				96,97

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Figure 1. Experience-dependent effects on adult neurogenesis in the hippocampus, as well as on cognition and anxiety-like behavior. This figure summarizes findings from studies examining the effects of experiences with different emotional valences on adult neurogenesis and behaviors associated with the hippocampus. Experiences are grouped as negative, positive, or mixed valence. Red boxes indicate negative effects (reduced adult neurogenesis, impaired cognitive performance, and less anxiety-like behavior); blue boxes indicate positive effects (increased adult neurogenesis, improved cognitive performance, and more anxiety-like behavior); yellow boxes indicate no change; cross-hatched boxes indicate no data. Negatively valenced experiences are associated with reduced adult neurogenesis (red) and impaired cognitive performance (red), but more anxiety-like behavior (blue). Positively valenced experiences are associated with increased adult neurogenesis (blue) and improved cognitive performance (blue), but less anxiety-like behavior (red). Mixed valence experiences may lead to mixed outcomes, such as reduced adult neurogenesis (red) and less anxiety-like behavior (red), or no effect (yellow), presumably due to the additive nature of experiences of opposite valence. It seems unlikely that these null outcomes reflect that complex experiences have no effects on the brain and behavior. Sample references are provided for each effect [5,8,18,19,21,22,34,35,39,74–76,82–97].

Box 1. Glial cells: overlooked participants in experience-dependent change

Neuroscience has focused intensively on neurons, largely ignoring or discounting glial cells. This is particularly true for studies of adult neurogenesis, wherein a fundamental component of progress in the field has been ruling out the glial nature of new cells. A growing body of evidence suggests that all three major classes of glial cell (astrocytes, microglia, and oligodendrocytes) have important roles in neuronal function. Astrocytes, the most numerous type of glial cell in the brain, are a heterogenous population that has been linked to basic functions such as response to damage, maintaining the blood–brain barrier, regulating local blood flow, and eliminating toxins from the brain during sleep [98,99]. A subpopulation of cells with astrocyte features also serves as stem cells that give rise to neurons in the adult brain [100]. Additionally, astrocytes have been implicated in synaptic plasticity [101], mood regulation [102], and possibly cognition [103]. Microglia, resident immune cells of the brain, are known to clean up neuronal debris, phagocytosing dead synapses as well as neurons [104], including those that were generated in adulthood [105]. Microglia are known to release cytokines that affect neurons, and some evidence suggests that these cells release molecules that influence synaptic plasticity and potentially learning [106]. Oligodendrocytes have a chief function in providing myelin for axon insulation, but more recent work has implicated this cell type in synapse elimination and, indirectly, in synaptic plasticity and cognition [107]. Studies indicate that astrocytes, microglia, and oligodendrocytes are influenced in number, size, and function by many of the experiences that alter adult neurogenesis, including stress and physical exercise [6,12,108]. It is clear that a complete understanding of how experience alters brain function will require focused attention on glial, as well as neuronal, plasticity.

Box 2. New neurons change along with old neurons

A complete understanding of how experience changes neural circuitry cannot focus exclusively on adult neurogenesis. For almost all types of experience that alter the number of new neurons, evidence also exists for other types of structural change, not only for neurons generated during adulthood, but also for neurons generated in development. Numerous studies have shown that stress reduces dendritic complexity, as well as the number of dendritic spines and synapses throughout the hippocampus [2,5,11]. Conversely, physical exercise, sexual experience, and intracranial self-stimulation enhance these same measures in the hippocampus [2,5]. Taken together with similar structural changes outside of the hippocampus, such as in the prefrontal cortex [2,11], these findings suggest global effects on neuron growth, whether suppressive or permissive, that must be included in attempts to understand how experience shapes cognition and brain function in general. Specific experiences also appear to alter different parts of the dendritic tree in ways that might sculpt the brain in a more tailored way [109]. The extent to which structural changes that occur with aversive or rewarding experience carry specific information that can guide future behavior in similar domains remains to be determined.

types of experience that have the opposite effect on adult neurogenesis and behaviors related to the hippocampus provide further indirect evidence in support of a causal relation (Figure 1).

Physical exercise effects on adult neurogenesis and hippocampal function

A large body of literature has explored the effects of physical exercise on adult neurogenesis in the hippocampus and found effects for both voluntary running on a wheel and forced running on a treadmill [5,18]. In general, the effects of physical exercise are opposite to those of stress. Whereas stress suppresses adult neurogenesis, physical exercise generally promotes it. However, there are exceptions to this observation. These include running in isolation and intense bouts of physically taxing exercise, both of which have a suppressive effect on adult neurogenesis, most likely due to stress [5,18]. Similar to the stress literature, physical exercise seems to have a global effect in the promotion of adult neurogenesis, targeting different stages, including cell proliferation, neuronal differentiation, and cell survival [5,18–20]. Running has been shown to enhance cell proliferation by shortening the cell cycle of progenitor cells [20,21]. It also enhances neuronal differentiation by hastening the expression of mature neuronal characteristics, and it prevents the death of new neurons [9,22–24]. In contrast to the effects of stress on adult neurogenesis, running produces fewer microglia in the hippocampus [24,25], an effect that may contribute to enhanced neuronal survival (Box 1).

Physical exercise has profound effects on the biochemical milieu of the hippocampus, because it is associated with

increases in levels of neurotransmitters and growth factors [18]. This is perhaps not surprising, given that physical exercise greatly improves blood flow and promotes angiogenesis, as well as the delivery of oxygen and nutrients to the brain [18,19]. Many of the molecules that are increased by running, including serotonin [26], insulin-like growth factor [23], and BdNF [27], have been causally linked to running-enhanced neurogenesis. Here again, these effects appear to be the converse of stress effects, which generally result in decreased levels of these molecules in the hippocampus [11,28,29]. One family of signaling molecules that does not follow this consistent pattern is glucocorticoids. Physical exercise is known to activate the hypothalamic–pituitary–adrenal axis, leading to increased levels of circulating glucocorticoids [5] and, paradoxically, increased neuronal growth in the hippocampus. Taken together, these findings suggest that other factors associated with running override the actions of elevated glucocorticoid levels.

One aspect of the running experience that may engage growth-promoting signaling molecules is that of reward. For laboratory rodents, voluntary running appears to be a universally rewarding experience, as evidenced by its ability to produce a place preference as well as physiological signs of withdrawal [30,31]. The rodent experience of running stands in contrast to the human experience of running, where the degree to which physical exercise is perceived as rewarding varies across individuals. This raises the possibility that the universal appeal of running in rodents is an artifact of living in captivity. However, a recent study showing that wild rodents voluntarily run in a wheel in the wild suggests that such behavior is naturally rewarding, as opposed to a side effect of living in captivity [32]. Although the distinction between the universality of the rewarding aspects of running between rodents and humans raises questions about the translational validity of these findings, studies of voluntary running in rodents may be generalizable to other experiences that individual humans are strongly motivated to pursue.

Consistent with the possibility that the rewarding aspect of running is responsible for neuronal growth, dopamine, a neurotransmitter central to reward learning

circuitry, has a positive influence on adult neurogenesis [33]. Additional experiences that are known to be rewarding, such as enriched environment living, sexual experience, intracranial self-stimulation (Figure 1), and cocaine administration, are known to promote adult neurogenesis [5]. However, an exception to this relationship can be observed with parenting behavior, which has a strong hedonic component but is associated with reduced, as opposed to enhanced, adult neurogenesis [34,35]. Given that parenting is a complicated experience comprising stress, enrichment, and profound hormonal changes [34], it is perhaps not surprising that its neurogenesis profile differs from those of more controlled rewarding experiences.

The behavioral changes observed in animals exposed to rewarding experiences that enhance neurogenesis also appear to be the opposite of what has been observed with stress (Figure 1). That is, improved performance on cognitive tasks involving the hippocampus has been reported following running [5,18], sexual experience [36,37], and intracranial self-stimulation [5,38]. Some of these experiences are also associated with reduced anxiety-like behavior [5,37,39]. The behavioral profile for parenting is similar to the adult neurogenesis findings in that it is mixed. Some studies report improved cognitive performance, whereas others do not [34,40–42].

A rich literature indicates that learning itself alters the number and development of new neurons in the dentate gyrus [43–45]. Manipulations carried out in these studies are more difficult to assign to aversive or rewarding categories because learning paradigms vary and most involve a combination of both. It is also difficult to assess whether training on a specific learning task alters learning on an altogether different task. Although proponents of mental training would suggest that it does, the literature on this subject is controversial and mixed [44].

Functional significance of new neurons

Adult-generated cells can be activated by a range of experiences, including exposure to a stressor, running, exposure to a novel environment, and recall of previously learned information [39,46,47]. Most of the experiences that activate new neurons are also known to alter the number of new neurons, as well as to change behaviors linked to the hippocampus. Taken together, these findings strongly suggest that new neurons participate in experience-dependent changes in hippocampal function.

These findings also raise the question of whether new neurons generated under specific experiential conditions are somehow geared toward the recognition of that particular experience. In other words, do these new cells represent a neuroanatomical mechanism for experience-specific learning or do they provide a more naïve pool of new neurons that are positioned to enable environmental adaptation in the future? In this regard, the literature presents a mixed set of findings. On the one hand, evidence suggests that new neurons generated during a period of spatial navigation learning are more likely to be activated by repeat exposure to relevant spatial cues [47,48]. On the other hand, evidence suggests that new neurons generated during running respond to a broad set of experiences relevant to the hippocampus, including stress, novelty, spatial cues, and running itself [39,46]. The proportion of new cells that respond to these cues does not differ based on whether the cells were generated during running or sedentary living, indicating that the cells are not specifically tuned to the running experience.

Whether new neurons are tagged by the experiences surrounding their generation remains an open question, but recent evidence suggests that environmental conditions present during the time when new neurons are formed can influence later activation of those neurons. Specifically, new neurons generated during running are less likely to be activated by stress than are new neurons generated during sedentary living [39] (Figure 2). This lack of stress-induced activation seems attributable to increases in activity of GABA, a major inhibitory neurotransmitter, in the dentate gyrus itself [39], suggesting that plasticity in other neuronal populations that communicate with new neurons is important for understanding how hippocampal circuitry is changed by experience (Box 2). However, studies of experiential modulation of activity in new neurons have mostly used immediate early gene expression as a proxy for neuronal activity. Immediate early genes are rapidly increased in neurons when they fire action potentials, but this method is an indirect and general way of assessing neuronal activation that has poor temporal resolution and provides no information about how often a neuron is activated or its pattern of activation. Thus, it remains plausible that new neurons respond to general experiences with one activity pattern and to specific experiences related to the conditions under which they were produced with another, distinctly different, activity pattern.

A large body of literature has focused on understanding the function of new neurons, mostly without reference to experience-dependent change. Efforts to understand the behavioral impact of experience-dependent changes in adult neurogenesis need to consider both the function of the hippocampus itself and the electrophysiological properties of granule cells. Using a variety of technical approaches, most of which involve deleting new neurons, studies have addressed the behavioral consequences of new neurons directly. These studies have implicated new neurons in almost all of the known functions of the hippocampus, including its learning and memory capabilities [49,50], as well as in anxiety [50] and stress regulation [51].

Within the hippocampus, new neurons appear to be exclusively added to the dentate gyrus. Therefore, any discussion of the function of new neurons in the hippocampus must consider the function of this specific subregion. The dentate gyrus has been implicated in pattern separation, a computational process by which similar inputs are converted to more distinct outputs [52]. Behavioral pattern separation is used to describe discrimination between highly similar stimuli, usually in different contexts. New neurons have been implicated in pattern separation; cognitive behaviors reflecting this process can be altered by environmental stimuli that increase or decrease the number of new neurons in the dentate gyrus [53–58]. However, a recent detailed study using several methods to reduce the number of new neurons in the dentate gyrus failed to demonstrate any substantial deficit in learning or behavioral pattern separation [59]. Additional studies will be
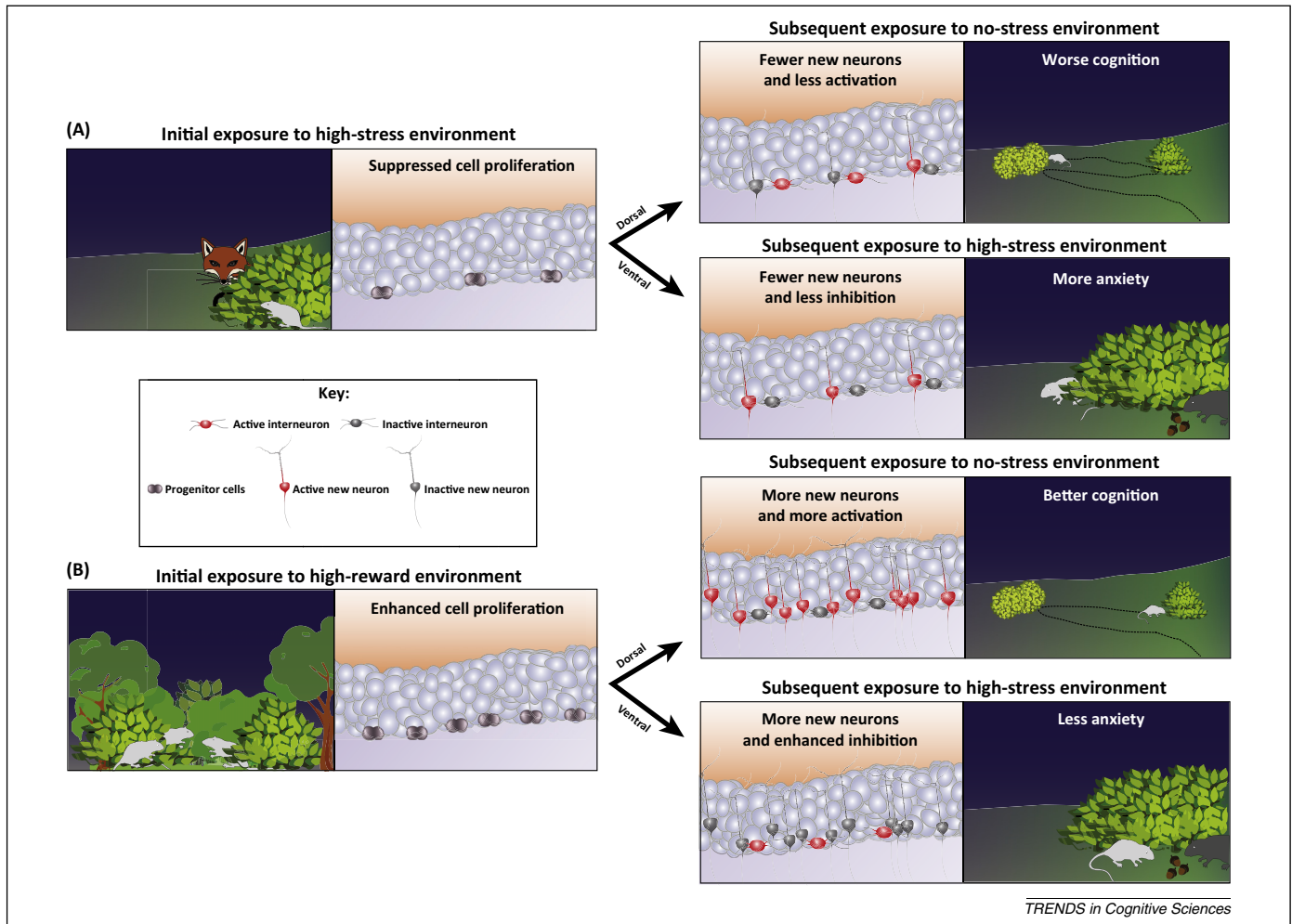
Figure 2. Experience modifies the dentate gyrus to prepare it for adaptive responses. This schematic depicts dentate gyrus-shaping scenarios rodents might encounter in the wild and their likely outcomes in terms of neuronal activation and behavior. **(A)** Initial exposure to a high-stress environment, such as one with predatory risk (in this scenario, a fox), suppresses adult neurogenesis throughout the dentate gyrus. At a subsequent time, under no stress conditions, the dorsal dentate gyrus would have fewer new neurons available to participate in spatial learning tasks, thus producing worse cognition (in this scenario, inability to remember food-foraging locations). Despite having fewer new neurons as well, the ventral dentate gyrus responds to stress with activation of such neurons, thus producing more anxiety (in this scenario, failure to forage for food in the presence of a novel nonthreatening conspecific). **(B)** Initial exposure to a high-reward environment, such as one providing ample opportunities for enrichment (in this scenario, prosocial interactions with conspecifics and a complex landscape to explore), enhances adult neurogenesis throughout the dentate gyrus. At a subsequent time, under no stress conditions, the dorsal dentate gyrus would have more new neurons available to participate in spatial learning tasks, thus producing better cognition (in this scenario, ability to remember food-foraging locations). Despite having more new neurons as well, the ventral dentate gyrus responds to stress with inactivation of such neurons, through the engagement of inhibitory neurons, thus producing less anxiety (in this scenario, willingness to forage for food in the presence of a novel conspecific).

needed to determine whether subtle differences in testing paradigms or baseline stress exposure underlie these discrepancies.

The involvement of new neurons in pattern separation may rely on their unusual electrophysiological properties, including enhanced synaptic plasticity, and a lower threshold for long-term potentiation compared with mature neurons [53,60]. The addition of new functional units, with their temporally dynamic profiles of functionality and excitability, and their differential responses to theta rhythms, may additionally separate information according to temporal features [53]. Such modulation of hippocampal circuitry may rely on the addition of highly excitable functional units to an otherwise silent network. In other words, new neurons may be given starring roles in the function of the dentate gyrus, at least until they transition into a state of maturity associated with their strong inhibition, when they become more like supporting characters.

Although only one type of neuron (i.e., the granule cell) is created through the process of adult neurogenesis in the dentate gyrus, regional differences in hippocampal function are likely to determine their role in behavior. The hippocampus can be divided into dorsal and ventral regions in rodents, or posterior and anterior regions, respectively, in humans [61]. These regions serve different functions; in rodents, the dorsal aspect has been associated with encoding spatial information, whereas the ventral aspect has been associated with anxiety and stress regulation [50,52,61,62]. Likewise, new neurons in the dorsal and ventral dentate gyrus may have distinct functions in terms of their behavioral output [50]. For example, selective deletion of new neurons in the dorsal, but not ventral, hippocampus impairs context fear conditioning. By contrast, selective deletion of new neurons in the ventral, but not dorsal, hippocampus prevents some of the anxiolytic actions of antidepressants [50]. However, this dissociation

seems to disappear under more challenging situations, such as in the presence of altered temporal cues or elevated levels of glucocorticoids, both circumstances in which new neurons throughout the dentate gyrus become capable of supporting tasks normally relegated just to a subdivision [50]. That is, under more taxing circumstances, regional specificity gives way to overall new neuron recruitment.

With regard to the regional specificity of new neuron function, experiential regulation of adult neurogenesis sometimes targets one subdivision more than it does others. For example, both stress and sexual experience seem to alter adult neurogenesis in the ventral dentate gyrus more profoundly than in the dorsal dentate gyrus [5,62–64]. Evidence indicates that new neurons in the ventral dentate gyrus are not only less numerous, but also undergo differentiation at a slower rate than those in the dorsal dentate gyrus [65]. This suggests that different time windows of sensitivity exist for experience-dependent effects on new neurons of one subdivision of the dentate gyrus versus another.

Despite being linked to different behavioral outputs, presumably because of different target sites of the dorsal and ventral hippocampus, new neurons throughout the dentate gyrus may use similar computational mechanisms. In this regard, pattern separation has been linked not only to the cognitive functions of the hippocampus, but also to its anxiety and stress regulation functions, in that these likely require the ability to distinguish familiar from novel, as well as safe from potentially threatening, circumstances [57]. In cases where the differences between known versus unknown or between safe versus unsafe situations are small, pattern separation may be critical for making accurate distinctions and setting a level of anxious behavior that is appropriate for the environment. It will be illuminating to ascertain whether a common computational mechanism exists for new neurons throughout the entire hippocampus. Regardless, the observation that certain experiences, such as stress, that regulate adult neurogenesis in turn activate new neurons and are directly related to new neuron functions, raises the possibility of an adaptive feedback loop that may shape the hippocampus to facilitate both cognitive and anxiety-like behavioral responses that are most appropriate to the environment.

Adaptive significance of new neurons

The relation between experiential regulation of new neuron number and the involvement of new neurons in functions related to that experience has been considered in previously described theories [37,57,66,67]. In particular, we have proposed that stress-induced decreases in new neuron formation may improve an animal's chances of survival by increasing anxiety and inhibiting exploration; impaired cognition may be a necessary trade-off for this benefit [37]. It is also worth considering the possibility that, although stress may impair learning, it may also have the advantage of diminishing forgetting, a phenomenon positively linked to the number of new neurons [68]. This may produce a maladaptive outcome under certain circumstances, as in the case of post-traumatic stress disorder, in which memories that should diminish over time do not [69]. Conversely, reward-induced increases in new neuron

number associated with diminished anxiety may facilitate exploration and learning, leading to greater reproductive success [37]. The ability of the hippocampus to continually produce a new pool of neurons, the numbers and organization of which are responsive to environmental conditions, strongly suggests that new neurons are a substrate for sculpting the brain to produce behaviors that are adaptive for the organism. Given that the past is often the best predictor of the future, a stress-modeled brain may facilitate adaptive responses to life in a stressful environment, whereas a reward-modeled brain may do the same but for life in a low-stress, high-reward environment. Thus, experience may optimize hippocampal circuitry through effects on adult neurogenesis by either priming a mode of avoiding punishment or seeking rewards. The influence of experience on hippocampal circuitry in adulthood may be a diminished version of what occurs during development when the base structure of the hippocampus is being formed. Studies have shown that early life experience can shape the developing hippocampus and also produce lasting changes in the rate of adult neurogenesis [70–72].

Although stress-induced decreases in adult neurogenesis may have adaptive benefits, they remain potentially problematic for adaptive flexibility; if an organism encounters stressful circumstances, is it doomed to avoid situations that could be rewarding even when circumstances change? Such a behavioral bias could hardly be considered optimal, except in the short term. Recent studies suggest that a more flexible adaptation scheme is engaged in certain challenging situations. As discussed above, the region-specific involvement of new neurons in cognitive versus anxiety-related functions appears to dissipate in favor of overall hippocampal involvement when conditions are especially challenging [50]. In the laboratory, stress-induced inhibition of adult neurogenesis has been shown to be reparable in that new neuron production typically returns to normal once the stressful period ends (Figure 3). By contrast, repeated stress produces continued reduction in adult neurogenesis and, ultimately, the emergence of depressive-like symptoms, including anhedonia, along with heightened anxiety [73] (Figure 3). Such a scenario could represent processes that are engaged under pathological conditions and may be somewhat akin to what humans experience when exposed to repeated traumatic stress. Thus, when aversive experiences far outnumber rewarding ones in both quantity and intensity, the system may reach a breaking point and produce a maladaptive outcome. However, it seems clear that the typical response to stress is one of resilience in which adjustments in hippocampal structure and function to better suit the environment do not interfere with the ability to take advantage of rewarding opportunities that may arise in the future.

Consideration of the adaptive significance of adult neurogenesis raises questions about conditions that animals typically experience in the wild. Meaningful tests of new neuron function may require different experimental approaches, including a focus on more naturalistic environments that provide cues necessary for naturally occurring levels of brain plasticity.
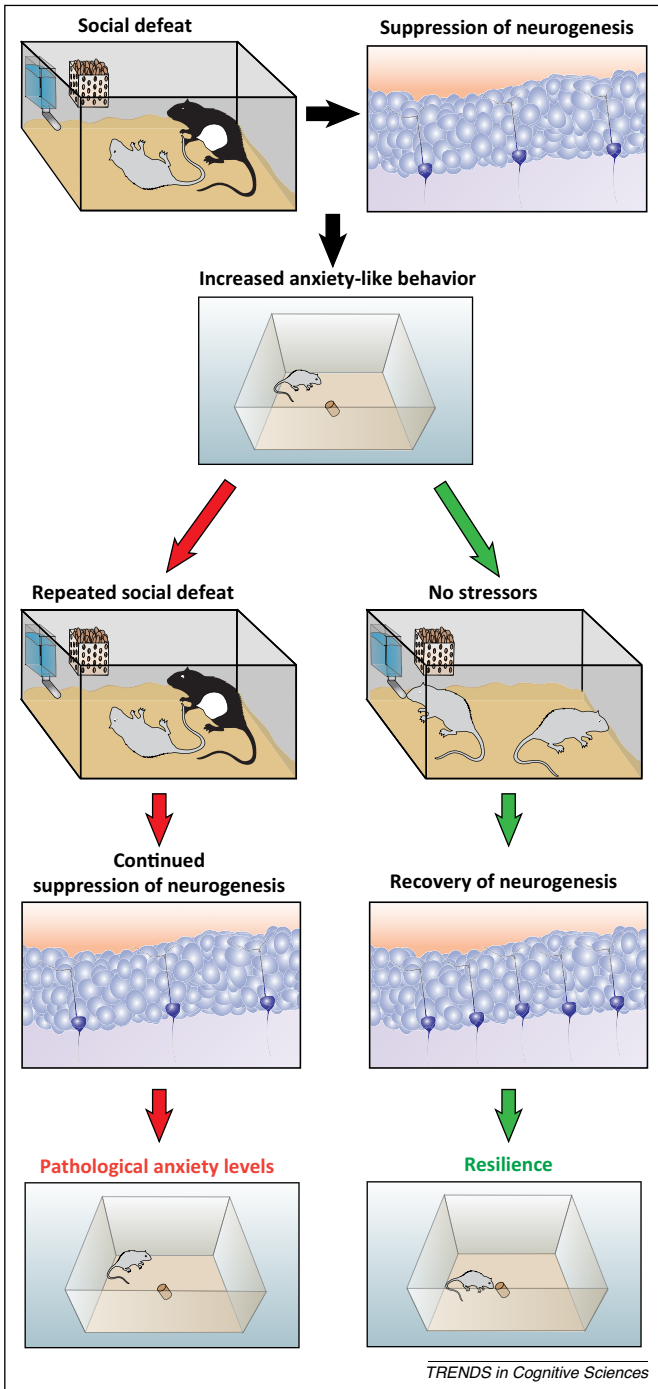
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Figure 3. Stress-induced modifications in hippocampal circuitry lead to resilience or pathology depending on the duration of stress exposure. This schematic shows the brain and behavioral response to short-term versus persistent stressor exposure. Short-term exposure to laboratory stressors, such as social defeat, suppresses adult neurogenesis. These changes are associated with increased anxiety-like behavior, such as avoidance of novel food in a novelty suppressed feeding task. If conditions change and no further stressors are introduced, adult neurogenesis levels should recover and increased anxiety subsides. If stressful conditions continue, adult neurogenesis will be further suppressed and anxiety-like behavior will persist. This outcome is particularly disadvantageous if conditions become safe, because persistent anxiety could prevent acquisition of rewards that would help restore adult neurogenesis levels.

New neurons in the real world

There is little doubt that adult neurogenesis and new neurons themselves are sensitive to experience. However, laboratory studies from which this conclusion has been drawn typically investigate adult neurogenesis in animals that are essentially devoid of most experiences that would have been present during mammalian brain evolution. This potential confound raises the question of whether studying an experience-dependent process under controlled laboratory conditions provides information with any relevance to understanding the brains of animals living in their natural habitats. Animals in the wild have complex, challenging, and stimulating lives, whereas those living in standard laboratory settings have limited, static lives lacking stress and stimulation (Figure 4). Furthermore, animals in the wild have varied experiences that can serve to accentuate individual differences in brain and behavior, whereas those living in standard laboratory settings have similar experiences that undoubtedly narrow the range of brain and behavioral measures. Research exploring the effects of stress on adult neurogenesis would suggest that laboratory control animals, with their relatively stress-free existences, have more new neurons than their wild-living counterparts. Conversely, research exploring the effects of physical exercise on adult neurogenesis would suggest that laboratory control animals, with their sedentary lifestyles, have fewer new neurons than their wild-living counterparts.

Clearly, living in the wild involves exposure to multiple experiences known to alter adult neurogenesis. Some studies have sought to address this issue by combining exposure to positive and negative regulators of adult neurogenesis (e.g., stress and running or stress and sexual experience) and have found the effects seem to cancel one another out (Figure 1). That is, running or sexual experience reverses stress-induced suppression of neurogenesis, such that there is no net change compared with neurogenesis in control animals [74–76]. Perhaps in a similar vein, wild-caught rodents exposed to a running wheel do not exhibit increased adult neurogenesis [77], possibly due to the combined actions of the stress of captivity and physical exercise on this population. Does the lack of change in overall new neuron number in laboratory animals exposed to two experiences with seemingly opposite emotional valences suggest that adult neurogenesis and, indeed, the hippocampus itself, remains unchanged by these experiences? It is possible that experiential regulation of adult neurogenesis only matters for hippocampal function when the emotional valence of the overall experience of an organism is highly biased in one direction or the other, as opposed to mixed. However, this seems unlikely, especially given the fact that the number of new neurons is only one aspect of adult neurogenesis that can be modulated by experience. To better understand how new neurons refine brain function in animals living in the wild, studies examining adult neurogenesis under conditions that are as similar to the wild as possible would be useful.

Enriched environment studies in the laboratory are important steps in the right direction toward understanding adult neurogenesis in the brains of animals living natural lives in that they increase complexity and provide opportunities for cognitive, social, and physical challenges relative to laboratory cage controls. However, these studies typically work to minimize competition among conspecifics and almost always involve animals of one sex, a highly unnatural social arrangement for rodents. The use of a
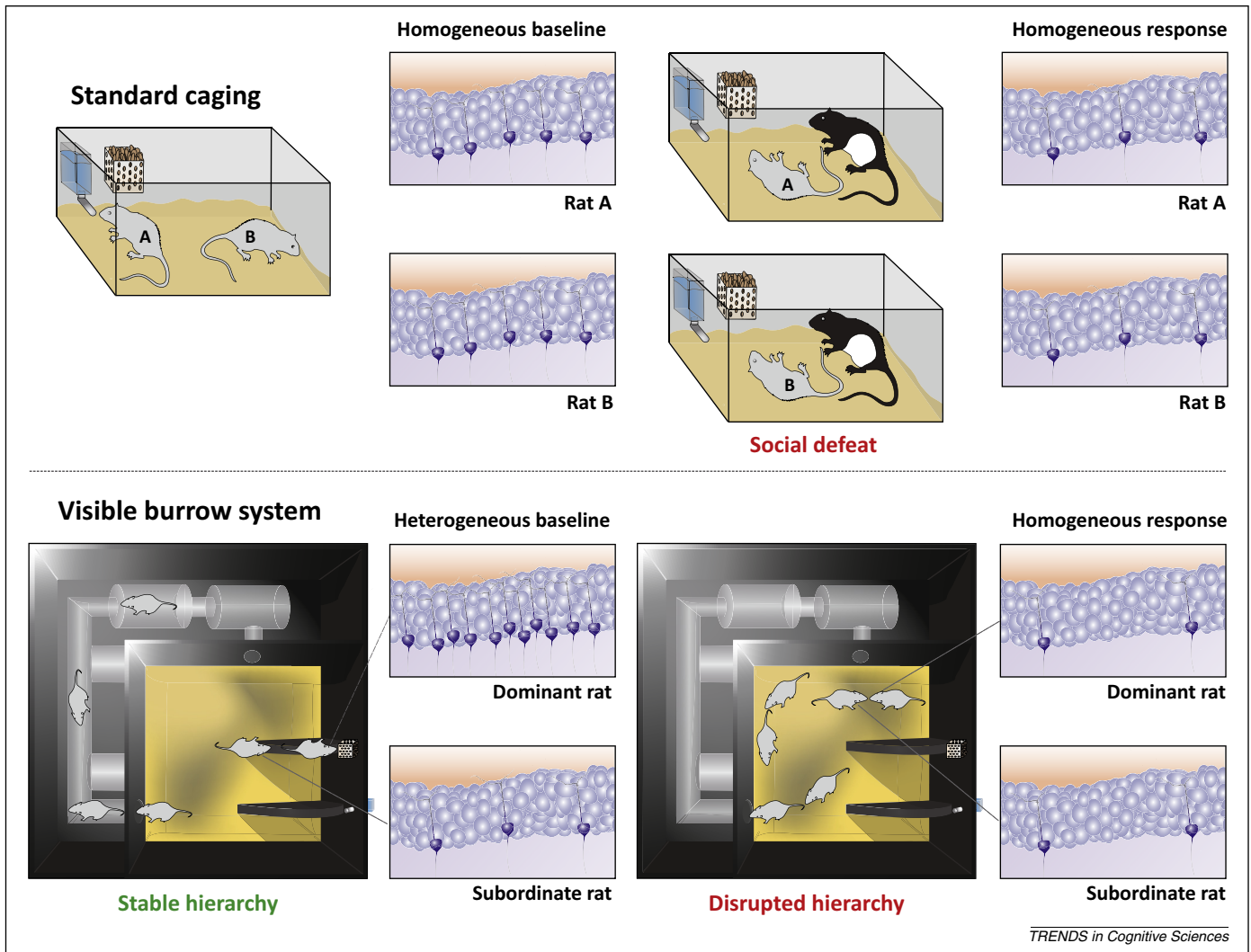
Figure 4. More naturalistic settings alter the adult neurogenesis profile in the hippocampus. Schematic diagrams showing the effect of different types of laboratory housing (standard caging or visible burrow system) on new neurons in the dentate gyrus at baseline and after social defeat stress. Standard housing produces a homogeneous adult neurogenesis baseline and a homogeneous stress-induced adult neurogenesis suppression (both rat A and B have the same response). This uniformity may be an artifact of living in artificial laboratory housing. In a visible burrow system, living in a stable social hierarchy produces a heterogeneous baseline with more neurogenesis in the dominant compared with subordinate rats. This community profile of adult neurogenesis and its related behaviors is more likely to reflect that of animals living in the wild. This range of individual differences can be eliminated by an extreme intervention imposed on the entire group. Social hierarchy disruption, which produces increased aggression, results in a substantial decline in new neuron number in all animals, regardless of their social position.

visible burrow system can provide a hybrid between the wild and the enriched environment laboratory setup [78]. The visible burrow system, a structure comprising tubes, chambers, and an open field, has enabled researchers to recreate the conditions that allow for the production of dominance hierarchies that rats naturally form in the wild, replicating many of the stressors and rewards that accompany this social lifestyle. Social experiences, including dominance hierarchy formation, engage a variety of neural systems, including those that underlie learning and memory and decision-making. As such, these scenarios provide a more realistic model for studying functional modifications in neuron production and recruitment.

Previous studies have shown that, when mixed-sex rats live in a dominance hierarchy in a visible burrow system, individual differences emerge in the number of new neurons in the dentate gyrus. Dominant male rats produce more new neurons than do subordinate male rats. A similar relation between dominance status and adult neurogenesis has been

demonstrated for baboons [79]. For Sprague–Dawley rats at least, this outcome is not directly related to stress, because glucocorticoid levels do not differ between dominants and subordinates [5]. These findings are illuminating because they involve adult neurogenesis in a more realistic setting that combines previously isolated stimuli, such as social interaction, physical exercise, environmental enrichment, sexual experience, and social stress. These findings also suggest that animals living in similar circumstances have different levels of adult neurogenesis depending on individual differences in the degree to which they engage in certain behaviors.

Although the use of the visible burrow system enables researchers to observe adult neurogenesis in a naturalistic setting, it also allows for ethologically relevant perturbations of this setting. In the wild, dominance hierarchies can be destabilized if a dominant animal dies or leaves the community. This scenario can be replicated in the laboratory by interchanging dominants from stable hierarchies, a

manipulation that disrupts the social order and produces renewed fighting. Regardless of social position before the disruption, animals living in a disrupted social hierarchy show decreased survival of adult-born neurons [80]. Thus, social disruption trumps the individual differences in new neuron number that emerge as a result of stable hierarchy living. As mentioned above, conditions under which neurons are generated may 'program' these neurons to be activated by and functionally involved in tasks of the same type. The extent to which neurons generated during a disrupted social experience are activated by, and involved in, stress regulation and social behavior remains unknown. Nonetheless, the visible burrow system presents an unusual opportunity to explore the effects of complex experiences on adult neurogenesis and hippocampal function in a meaningful social setting that more closely mimics wild habitats than most laboratory conditions. However, the utility of this approach requires the use of appropriate species and strains of animals to minimize physical aggression and to easily distinguish among animals so that their behavior can be analyzed accurately. For example, male mice may be too aggressive for such experiments and pigmented rats may be too difficult to distinguish from one another (albino rats can be tagged with dye in easily distinguishable patterns). Furthermore, experiments designed to increase individual differences require larger *n* sizes to obtain enough power for meaningful statistical analyses. In effect, such environmental living conditions make studies on experimental animals prone to some of the same practical limitations as those of studies on humans, which may not be optimal for many experimental questions.

Studies have shown that the human hippocampus exhibits a substantial amount of adult neurogenesis [4] and that neuronal growth in the human hippocampus may be stunted by stress [81] and stimulated by physical activity [19]. Although such results in humans are severely limited by technical and ethical constraints, they are nonetheless encouraging indicators that laboratory research on adult neurogenesis in experimental animals may be on the right track toward understanding how experience alters plasticity in the human brain. Taking findings from laboratory animals to the next level by exploring complex social interactions in settings that maximize individual variability, a hallmark of the human experience, is likely to be especially illuminating.

Concluding remarks

For centuries, philosophers have argued over the extent to which biology is destiny, or, to what extent experience can change the brain and behavior. Discoveries of experience-dependent change in adult neurogenesis and other forms of plasticity suggest that the brain can refine its structure and function based on experience. Encountering environments in which exploration is rewarding seems to lead to a brain primed for exploration and improved cognition through enhanced neurogenesis and decreased anxiety. By contrast, punishment and stress seem to lead to a brain primed to prioritize safety and avoidant behavior over cognitive optimization and increased production of new neurons.

Given contemporary views about the need to reduce stress and increase physical activity to optimize human brain health, it may be that Ramon y Cajal's claim about the ability to sculpt one's own brain, by controlling one's experiences, has become a scientific and cultural reality. Seeking out rewarding experiences and avoiding stressful experiences may help each individual optimize his own brain. However, this is not always easy or even possible; the real-world scenarios that humans face most often involve a complement of stressful and rewarding conditions. Tightly controlled laboratory studies of adult neurogenesis have been informative, but new data suggest qualitative differences in the type and complexity of experiences that affect adult brain plasticity in the hippocampus. Naturalistic experimental scenarios may prove invaluable in this regard, to understand the scope of this neurobiological process and its functional consequences.

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