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Hippocampal neurogenesis and forgetting

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The hippocampus is thought to automatically encode all experience, yet the vast majority of our experiences are not remembered later. Although psychological theories have postulated the existence of decay processes for declarative memory, the corresponding neurobiological mechanisms are unknown. Here we develop the hypothesis that ongoing hippocampal neurogenesis represents a decay process that continually clears memories from the hippocampus. As newborn granule cells integrate into established hippocampal circuits, they form new input and output connections over the course of several weeks. Because successful memory retrieval relies on reinvoking patterns of activity that occurred at the time of encoding (pattern completion), neurogenesis-induced remodeling of hippocampal circuits incrementally reduces the likelihood that a given retrieval cue will reinvoke a previously stored pattern.

Introduction

In the 1960s Altman published pioneering studies showing that neurogenesis persists in the subgranular zone of the hippocampus beyond development and into adulthood [1–3]. Although this field largely lay dormant for the better part of the next three decades, interest was rekindled in the 1990s when new immunohistochemical methods were developed that made it possible to definitively label newborn granule cells [4]. This prompted an explosion of studies asking whether and how new neurons contribute to hippocampal memory formation. These studies have taken advantage of increasingly sophisticated methods for ablating [5–7] or, more recently, disrupting the activity [8,9] of new neurons, with the general premise of these studies being that new neurons are in some way 'good' for hippocampal memory. Accordingly, there is now an extensive (but sometimes messy) body of literature examining the impact of both increasing and decreasing adult neurogenesis on the formation of new hippocampal memories [10]. By contrast, here we consider the impact of ongoing neurogenesis on existing memories and propose a novel role for neurogenesis in forgetting.

New neurons and new memories

It is surprising that, almost without exception, previous studies have used essentially the same experimental design to examine the role of new neurons in memory. Neurogenesis levels are usually manipulated in adult rodents, and then, days or weeks later, the ability to form new hippocampus-dependent memories is evaluated. The typical result from these studies is that reducing neurogenesis impairs subsequent hippocampal memory formation. Conversely, increasing neurogenesis facilitates hippocampal memory formation in some cases. These anterograde effects were initially observed using a trace eyeblink conditioning paradigm [11], and subsequently shown across a range of other hippocampus-dependent tasks, including various forms of contextual and spatial learning [10]. Memory impairments are not universally observed following reduction of adult neurogenesis, however. Whether memory impairment is observed may depend on animal age at the time of neurogenesis reduction [12], the number of neurons targeted [13], the maturational stage of the targeted neurons at the time of learning [8,14], and the type of behavioral task used to assess learning and memory [15]. The finding that reducing neurogenesis does not always produce memory impairment may not be entirely unexpected because memory formation can probably be supported by developmentally generated granule cells alone [5].

How does neurogenesis regulate the ability to form new hippocampal memories? One idea is that neurogenesis enhances the process of pattern separation [16]. To encode distinct episodic memories, the brain must distinguish between different places in which these events occur [17,18]. Theoretical models originally proposed that this process of disambiguation of different places (pattern separation) is mediated by the entorhinal cortex–dentate gyrus (DG)–CA3 hippocampal circuit [19,20]. Within this circuit, the DG transforms similar overlapping patterns of activity from the entorhinal cortex into distinct population codes in the CA3. This model is supported by data from rodent *in vivo* recording studies [21–23]. In contrast to the DG (in which changes in context are signaled by changes in the firing rate of the same populations of neurons, i.e., a

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rate code), the CA3 region uses a population code (in which the same context shifts change the identity of the populations of CA3 cells that fire [22]). That the CA3 signals context shifts by engaging different populations of neurons is supported by data from cellular imaging studies using activity-dependent genes to identify neurons activated by the same versus different contexts [24].

Interestingly, recent studies suggest that adult hippocampal neurogenesis enhances memory formation by modulating the efficiency of pattern separation. Using the activity-dependent gene mapping approach, Niibori and colleagues showed that reducing adult neurogenesis (via either chemical or genetic approaches) degraded the ability of the CA3 to separate patterns via population coding (there was a large overlap in the population of CA3 neurons that were active in similar contexts) [25]. The finding that a reduction in adult neurogenesis impairs the ability of the CA3 to separate patterns at the circuit level is mirrored by results at the behavioral level that showed that reducing adult neurogenesis produces deficits in visual, context, and spatial discrimination [25–30]. Conversely, increasing adult neurogenesis by promoting the survival of newborn cells facilitates spatial and contextual discrimination, perhaps by enhancing pattern separation [28]. Similarly, silencing the output of developmentally generated DG neurons only (thereby shifting the balance of the DG towards a more immature state) also facilitated spatial and contextual discrimination [9]. Together these studies suggest that neurogenesis positively modulates the ability of the hippocampus to form distinct memories of different episodes by facilitating pattern separation [16].

New neurons and old memories

This focus on the anterograde effects of manipulating adult neurogenesis on memory has come at the expense of an examination of potential retrograde effects: how does the integration of new neurons into existing hippocampal circuits impact information already stored in those circuits? The integration of newborn neurons into the hippocampus follows a stereotypical course [31]. Division of progenitor cells in the subgranular zone gives rise to new cells that migrate into the innermost part of the granule cell layer. The vast majority of these cells differentiate into neurons, extending apical dendrites into the molecular layer of the hippocampus and mossy fiber axons toward the CA3 region. Input and output synapses begin to form on adult-generated neurons at ~2.5 weeks, and synaptic integration of these neurons into hippocampal circuits continues over the next several weeks [8,32–35]. During this integration process, new neurons compete with existing granule cells for inputs and outputs, establishing new synaptic connections that either coexist with, or even replace, established synaptic connections in both the DG and CA3 (Figure 1) [36–38]. Although the time-course of integration of new neurons is largely invariable, the proliferation and survival rates of new neurons may be regulated by several factors, including stress, exercise, environmental enrichment, drugs of abuse, and age [31,39].

In addition to this direct structural remodeling, the integration of new neurons into the hippocampus may indirectly modify the strength of established synaptic connections. Immature neurons are more excitable than their mature counterparts [32,33,40]. Therefore, newly generated granule cells fire more action potentials to a given stimulus than mature granule cells do. Accordingly, the addition of new neurons to an established DG–CA3 circuit might lead to an overall increase in circuit excitation. Networks strive to maintain homeostasis by altering network and cellular properties to counteract perturbations. Therefore, the addition of new highly excitable cells to this circuit would likely engage these circuit-wide compensatory changes to regulate network stability [41]. These mechanisms may include a decrease in the intrinsic excitability of existing DG and/or CA3 neurons (e.g., by decreasing sodium currents and/or upregulating fast-inactivating and calcium-activated potassium currents [42–45]) or neuron-wide synaptic scaling (e.g., loss or endocytosis of post-synaptic GluA2 AMPA receptors [46,47]) which may eventually lead to silencing of some synapses [48]. Therefore, in addition to generating new synaptic connections, the addition of new neurons may alter the strength of existing hippocampal connections.

How does this continuously evolving hippocampal landscape impact previously stored information? Computational models predict that the addition of new neurons degrades existing memories. These models have typically used a simple, three-layer architecture (an input [entorhinal cortex], middle [DG] and output [CA3] layer), with neurogenesis modeled by either replacing mature neurons or adding new neurons to the middle DG layer [48–52]. Mature dentate neurons constitute a critical component of the memory trace in these models, so replacement of these essential neurons leads to memory degradation. Results from experimental studies, however, indicate that neurons that are committed to a memory trace may actually have a survival advantage [53], suggesting that these mature memory-committed neurons are not likely to be replaced. However, these computational models still predict memory loss when new neurons are simply added to the existing circuit, rather than replacing existing neurons [48–50]. Therefore, these neurocomputational data predict that adult neurogenesis increases forgetting.

New neurons and forgetting

Successful memory retrieval requires intact encoding, consolidation, and retrieval. Some instances of memory failure are simply due to ineffective encoding (such as not attending to where one puts one's glasses; a type of memory failure common during multitasking). However, as Tulving emphasized, forgetting is 'the inability to recall something now that could be recalled on an earlier occasion' [54]. More precisely, forgetting may be defined as the inability to access information that was (i) successfully encoded and (ii) could previously be retrieved by the same retrieval cue that now leads to retrieval failure [55]. Within this definition, forgetting can be due to either a failure of memory consolidation or problems that arise as a consequence of the act of retrieving itself (i.e., retrieval-induced forgetting [56]). Notably, even a failure of memory consolidation would ultimately be manifest as unsuccessful memory retrieval.

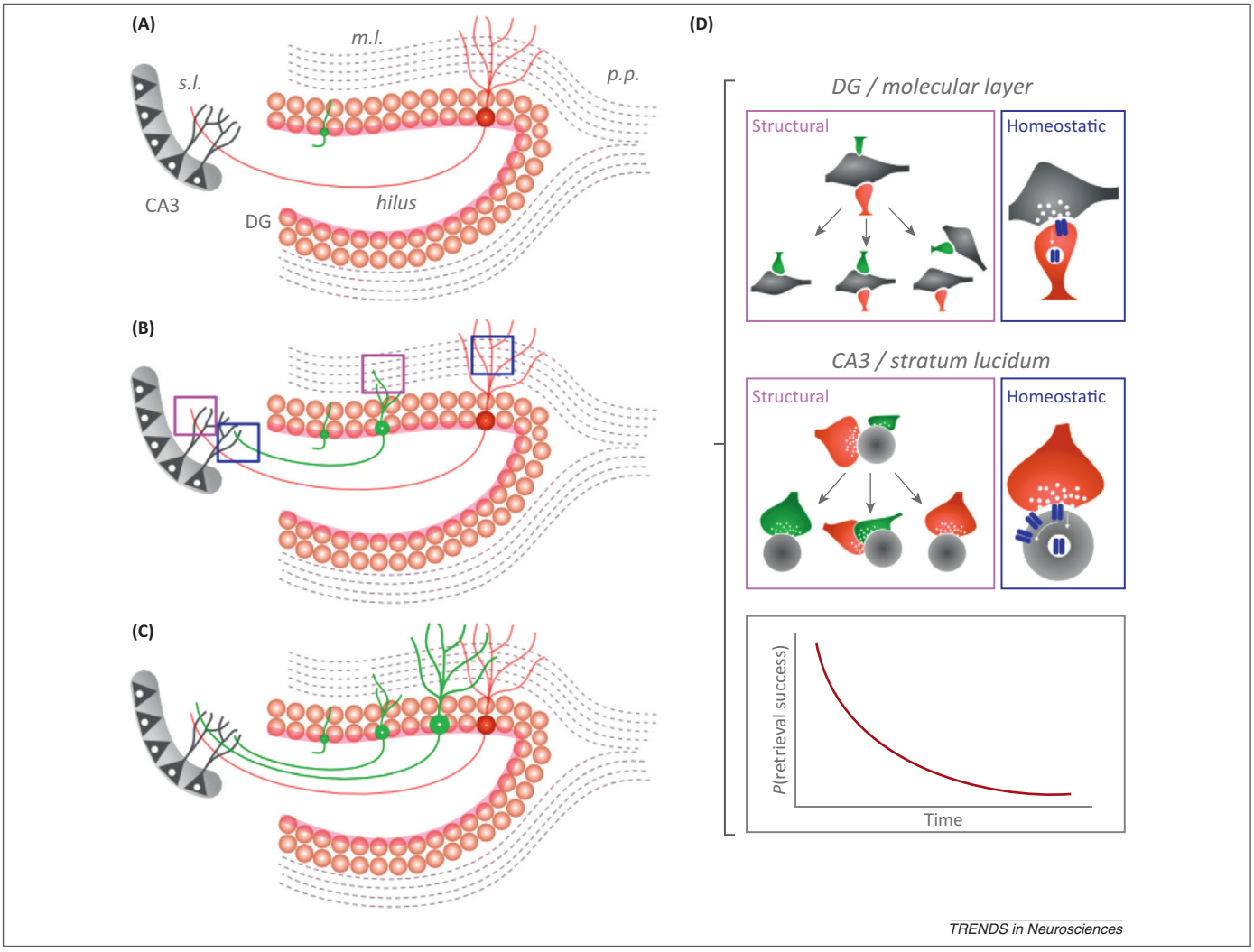

Figure 1. The integration of new neurons into the dentate gyrus induces forgetting of previously acquired (old) memories. **(A)** New dentate granule cells (DGCs, green) integrate into an established DG circuit in which existing DGCs (red) receive perforant path (p.p.) inputs from the entorhinal cortex and send a mossy fiber axon toward pyramidal cells in the CA3 (gray). **(B)** New DGCs form input and output connections, starting at ~2.5 weeks of age. **(C)** Neurogenesis-induced remodeling of hippocampal circuits accumulates over time. **(D)** The integration of new DGCs produces both direct structural (pink insets) and indirect homeostatic (blue insets) changes in hippocampal circuits. New neurons compete with existing granule cells for inputs and outputs, establishing new synaptic connections that either coexist with or even replace established synaptic connections in both the DG molecular layer (m.l.) and CA3 stratum lucidum (s.l.). Because these new DGCs are more excitable than their mature counterparts, the addition of new neurons to an established DG–CA3 circuit might lead to an overall increase in circuit excitation. These changes are counteracted, for instance, by decreasing the intrinsic excitability of existing DG/CA3 neurons (top) or neuron-wide synaptic scaling (e.g., loss/endocytosis of post-synaptic GluA2 AMPA receptors) (middle), which may eventually lead to silencing of some synapses. In this way, the integration of new neurons into an existing hippocampal circuit produces ongoing changes to hippocampal circuitry, resulting in a decrease in the likelihood of successful pattern completion (memory retrieval succcess) over time (bottom).

In the brain, successful memory retrieval is thought to reflect reactivation of the patterns of neural activity present at the time of memory encoding (a process known as pattern completion) [57–60]. Neurally, therefore, forgetting may be defined as the failure of a retrieval cue to reinvoke the pattern of neural activity present at encoding. Accordingly, we propose that the incremental integration of new neurons into existing hippocampal circuits promotes forgetting by reducing the ability of a once-effective retrieval cue to reinvoke the same pattern of activity present during memory encoding. Thus, adult neurogenesis would promote a failure of pattern completion and therefore unsuccessful memory retrieval.

Types of forgetting

Although forgetting has received scant attention in neurobiological studies of memory (for some notable exceptions, see [61–64]), within the traditions of experimental psychology, forgetting has received significantly more consideration.

The most common form of forgetting studied in the psychological laboratory (although probably not the most common form of forgetting in daily life) is a type of retrieval-induced forgetting known as cue overload [65]. As stated above, successful memory retrieval rests on the availability of an effective retrieval cue. The most effective retrieval cue is one that is uniquely associated with a memory episode or trace. However, some cues acquire associations with multiple memories. The greater the number of associations a cue acquires (i.e., the more overloaded a cue becomes), the less efficient it becomes at retrieving the desired memory [66]. From this perspective, some forgetting occurs because of interference present at the time of retrieval. Similar items tend to be associated with the same cue, so it is predominantly information that is similar or related in content that induces interference at the time

of retrieval. Cue overload may increase with time (because there are more opportunities for a cue to acquire new associations). However, because this type of forgetting is tied to the retrieval process itself, it does not occur in the absence of any retrieval attempt.

Ongoing neural activity that takes place outside of retrieval represents an alternative source of interference that might contribute to forgetting. In particular, Wixted has proposed that the process of forming new memories, and associated changes in synaptic weights, may create retroactive interference by degrading previously encoded information [65,67]. That is, new learning changes the hippocampal circuitry such that a retrieval cue would be less likely to reproduce the pattern of neural activity required for successful memory retrieval. Consistent with this hypothesis, induction of long-term potentiation (LTP) in the hippocampus, which would change synaptic weights, weakens both previously established LTP [63] and hippocampal memory [68]. In contrast to retrieval-induced forms of forgetting such as cue overload, this type of forgetting is indifferent to memory content: forgetting occurs regardless of the similarity between the previously encoded and current experience (as long as both experiences engage a similar neural circuit). Thus, this forgetting reflects a form of nonspecific retroactive interference[65], with the formation of new memories (and the corresponding changes in synaptic strength) weakening any existing memory that (i) engages the same or overlapping hippocampal circuits and (ii) has not yet been fully consolidated.

Neurogenesis and nonspecific retroactive interference

We propose that ongoing neurogenesis represents an additional distinct form of forgetting that also depends on nonspecific retroactive interference. Similar to the modification of existing synaptic connections produced by the formation of new memories, the integration of new neurons into hippocampal circuits adds new and modifies existing synaptic connections. The consequence of this structural interference is that the circuitry of the hippocampus is continuously evolving, and so the likelihood that a retrieval cue will be able to reinvoke the same pattern of activity within this circuitry declines as a function of time. From this perspective, neurogenesis may be viewed as an unrelenting decay process that impacts all hippocampus-dependent memories, regardless of content.

Accordingly, neurogenesis-induced forgetting shares some, but not all, features of the learning-induced forgetting process described by Wixted [65]. Importantly, both the neurogenesis-induced forgetting we describe and the learning-induced forgetting described by Wixted are not driven by any retrieval process and therefore proceed even in the absence of retrieval attempt, making both processes distinct from cue-overload-induced forgetting. Furthermore, unlike cue overload, both forms of forgetting are agnostic to memory content (i.e., the degree of similarity between encoded and current experience is irrelevant). Where neurogenesis- and learning-induced forgetting differ is in their respective time-courses. Synaptic strengthening following learning (i.e., cellular consolidation in the hippocampus) begins within minutes and these changes stabilize within hours [69]. Therefore, the form of synaptic over-writing induced by new learning should degrade only labile (not fully consolidated) memories within this relatively brief time window. By contrast, remodeling of hippocampal circuits via the integration of new neurons is a prolonged process. In the DG, several thousand new granule cells are generated daily. Each new cell projects a mossy fiber that reaches the CA3 region within approximately 2 weeks, contacting 11–15 pyramidal cells [70]. Therefore, the likelihood of retrieval failure due to neurogenesis-induced remodeling increases as circuit changes accumulate. In this way, forgetting slowly emerges over time (most likely over days and weeks) and impacts memories beyond the initial phase of cellular consolidation.

At present, there are no direct tests of the proposed role of neurogenesis in forgetting, with perhaps one exception. High-frequency stimulation of perforant path induces LTP of perforant path–DG synapses. Although this form of LTP is maintained *in vivo* over several days, it weakens over time and returns to baseline after approximately 2 weeks. Remarkably, reduction of neurogenesis during this period sustains this form of LTP [71], suggesting that decreasing neurogenesis reduces forgetting of LTP. These findings are consistent with the idea that neurogenesis-induced remodeling of hippocampal circuits is incompatible with stable information storage.

Forgetting versus consolidation

Although much of what we experience is ultimately forgotten, memories for some events persist. In the face of continuous neurogenesis-dependent decay, how might some memories survive? In our proposal, the fate of any memory depends on the outcome of a competition between two opposing processes: memory trace consolidation (i.e., the cellular and systems processes that promote stabilization of traces within hippocampal and extra-hippocampal circuits [72–76]) and memory trace decay (i.e., ongoing neurogenesis and other related decay mechanisms [64] that weaken traces).

Consolidation and neurogenesis are regulated in multiple ways, and so the balance between these two opposing processes is highly dynamic. For instance, memory consolidation is thought to be driven by trace reactivation that occurs during retrieval or off-line replay (e.g., during sleep) [77]. The reactivation of a trace is thought to lead to a proliferation of traces within the hippocampus and/or stabilization of traces within the cortex [78,79]). In this way, more frequently reactivated traces are strengthened. Levels of neurogenesis are also highly regulated. For example, a large number of factors have been identified that robustly downregulate neurogenesis, including stress, drugs of abuse, and diet. Conversely, other factors promote proliferation and/or survival of new hippocampal granule cells, including exercise, environmental enrichment, and serotonin-specific reuptake inhibitors (SSRIs) [31,39]. We predict that memories survive if consolidation processes outstrip neurogenesis-induced decay. Such a reactivation-based account of consolidation can be thought of as a sort of 'use it or lose it' (or, more accurately, reactivate it or lose it) Darwinism for memory traces, with only the most frequently reactivated memories prevailing and less frequently reactivated memories eventually being over-written and forgotten. Interestingly, during

Box 1. Forgetting during infancy

Typically, our earliest memories are from when we were 4 or 5 years of age. Sigmund Freud was one the first to pay attention to this phenomenon of infantile or childhood amnesia, noting that his adult patients rarely recalled any memories from their earliest childhood years. Since the time of Freud, infantile amnesia has been studied using more empirical approaches and across cultures. A near universal pattern emerges: adults typically have no memories from the first three years of life, and inconsistent memory for events between the ages of 3 and 7 [83]. Psychological theories of infantile amnesia emphasize the co-emergence of language or sense of self-identity with the ability to form persistent memories for episodes. However, experimental animals also exhibit pronounced forgetting during infancy, so the phenomenon cannot be accounted for using purely human concepts. Within the framework proposed here (and expanded upon elsewhere [80]), the high levels of neurogenesis during infancy are incompatible with stable memory storage, with all hippocampal memories destined to fade as they succumb to neurogenesis-induced decay. Interestingly, not all animals studied exhibit infantile forgetting. For instance, in precocial species such as guinea pigs, the vast majority of granule cells are generated pre- rather than postnatally. Therefore, during infancy, levels of neurogenesis-induced remodeling in the hippocampus are much lower than in rats or mice. Corresponding to this more mature hippocampus, 5-day-old infant guinea pigs are able to acquire and retain spatial discrimination memories as well as adult guinea pigs can [84], and therefore do not display infantile amnesia.

infancy, episodic memories typically do not survive, a phenomenon known as infantile or childhood amnesia. It has been proposed that the high rates of neurogenesis during this developmental stage are incompatible with stable memory storage (Box 1) [80].

Summary and predictions

Previous studies have examined the impact of manipulating levels of hippocampal neurogenesis on future memory formation. By contrast, here we focused on how the integration of newborn neurons into hippocampal circuits impacts existing memories, and therefore provided a new perspective on how ongoing neurogenesis impacts hippocampal memory function. We propose that ongoing neurogenesis produces an unrelenting form of retroactive interference that is indifferent to memory content. This hypothesis, founded mainly on anatomical and neurocomputational evidence, provides the basis for several behavioral predictions (Figure 2):

- In adult animals, increasing hippocampal neurogenesis should weaken existing hippocampal memories. More specifically, we predict that if neurogenesis is transiently increased after learning, the probability of successful retrieval will be reduced when animals are exposed to a previously effective retrieval cue. Forgetting might be even more pronounced when the retrieval cue is partial or impoverished (i.e., pattern completion should be impaired).
- Conversely, decreasing hippocampal neurogenesis may have a protective effect on existing hippocampal memories. More specifically, the probability of successful retrieval will be increased when animals are exposed to a previously effective retrieval cue. This beneficial effect may be more pronounced when the retrieval cue is partial or impoverished (i.e., pattern completion should be facilitated).

In this review, we focused on the retrograde effects of changing levels of neurogenesis. However, our model also makes predictions in the anterograde direction.

- When learning of new information conflicts with stored information, acquisition is slowed. Therefore, to the extent that we predict that increasing neurogenesis in adult animals weakens existing memories, it should also reduce this form of proactive interference. In other words, learning new information that conflicts with stored information may be facilitated in adult animals if

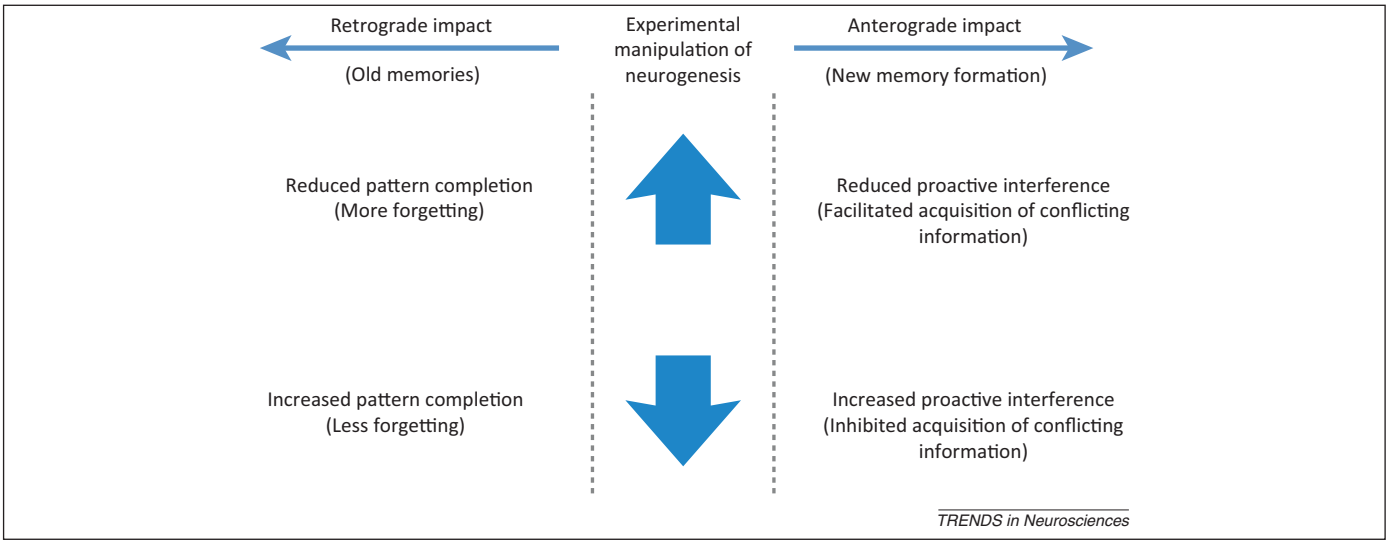

Figure 2. Model predictions. Our model predicts that experimental manipulation of neurogenesis impacts both old memories (retrograde effects) and new memory formation (anterograde effects). By remodeling hippocampal circuits, increasing neurogenesis is predicted to reduce the probability of successful retrieval of old memories (i.e., reduce the likelihood of successful pattern completion). At the same time, insofar as increasing neurogenesis induces forgetting of existing memories, acquisition of new information that conflicts with previously stored information will be facilitated in adult animals if neurogenesis is transiently increased after original learning (i.e., proactive interference will be reduced). Conversely, decreasing neurogenesis is predicted to increase the probability of successful retrieval of old memories (i.e., increase the likelihood of successful pattern completion). At the same time, insofar as decreasing neurogenesis protects existing memories, acquisition of new information that conflicts with previously stored information will be impeded in adult animals if neurogenesis is transiently reduced after original learning (i.e., proactive interference will be increased).

neurogenesis is transiently increased after original learning.

- Conversely, to the extent that we predict that decreasing neurogenesis in adult animals protects existing memories, it should also increase this form of proactive interference. In other words, learning new information that conflicts with stored information should be impeded in adult animals if neurogenesis is transiently decreased after original learning. From this perspective, although the retrograde effects are agnostic to memory content (similarity), the consequences of these retrograde effects on new learning are sensitive to content (i.e., conflict).

There has long been an appreciation that memory decay or clearance may be critical for normal healthy memory function [81,82]. This idea is motivated by the recognition that there are probably costs associated with remembering. These costs may include the energy expenditure required to maintain information storage over large spans of time, the consumption of finite storage space, and potential reductions in the efficiency or reliability of retrieval that might emerge with the proliferation of memory traces. Here we identify neurogenesis as a key regulator of memory decay in the hippocampus. Because forgetting or clearing of some types of information is beneficial, we argue that neurogenesis is indeed 'good' for memory, even with respect to the fate of previously stored information.

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