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Article title: Neurogenesis and pattern separation: Time for a divorce

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Abstract

The generation of new neurons in the adult mammalian brain has led to numerous theories as to their functional significance. One of the most widely held views is that adult neurogenesis promotes pattern separation, a process by which overlapping patterns of neural activation are mapped to less overlapping representations. While a large body of evidence supports a role for neurogenesis in high interference memory tasks, it does not support the proposed function of neurogenesis in mediating pattern separation. Instead, the adult-generated neurons seem to generate highly overlapping and yet distinct distributed representations for similar events. One way in which these immature, highly plastic, hyperactive neurons may contribute to novel memory formation while avoiding interference is by virtue of their extremely sparse connectivity with incoming perforant path fibers. Another intriguing proposal, awaiting empirical confirmation, is that the young neurons' recruitment into memory formation is gated by a novelty / mismatch mechanism mediated by CA3 or hilar back-projections. Ongoing research into the intriguing link between neurogenesis, stress-related mood disorders and age-related neurodegeneration may lead to promising neurogenesis-based treatments for this wide range of clinical disorders.

Introduction

Over fifty years ago, Altman and Das made the remarkable discovery of adult neurogenesis in the rodent brain.[1,2] This landmark finding called into question the long-held dogma that there are no new neurons created after birth. Not surprisingly, their discovery of neurogenesis met with intense scrutiny and scepticism. It took several decades of mounting evidence[3–9] to convince the scientific community at large that there is indeed ongoing genesis of new neurons in the adult mammalian brain. Since the 1990's, an explosion of research into neurogenesis has taken place, from basic mechanisms to functional implications. Adult neurogenesis has now been reported in a wide range of species from rodents to primates, including macaques[10] and humans[11–14].

Why was the phenomenon of adult neurogenesis so surprising? In short, the continuous addition of new neurons is the most extreme form of plasticity ever discovered in the adult mammalian brain. Consider what would happen if our entire brain remained neurogenic through the lifespan. Our memory circuits would be constantly re-wiring, forever erasing previously acquired knowledge and memories. Thus, under normal conditions, adult neurogenesis is restricted to very few mammalian brain regions, most notably, the dentate gyrus (DG) of the hippocampus and the olfactory bulb (OB).

In the DG of the adult rat, several thousand new granule cell neurons are generated every day[15], representing less than one percent of the total cell population. In adult humans, levels are even lower; about 700 new DG neurons are generated in each hippocampus per day, comparable to levels found in mice[14]. Although this represents only a small percentage of the total DG cell population being generated and/or renewed each day, the unique properties of the young DG neurons make them well poised to contribute to behaviour. The young (4-6 week old) DG neurons are hyper-excitable and highly plastic[16–19], so that they are recruited preferentially into novel memory traces[16,18] relative to fully mature DG neurons. Similarly, in the olfactory bulb of rodents, thousands of new granule cell interneurons are generated each day[20]. Relative to mature OB neurons, these newly generated young neurons exhibit an elevated and long-lasting responsiveness to new odours[21]. A key focus of ongoing research is how the brain is able to make use of these newly generated neurons to affect behaviour.

Adult Neurogenesis

Neurogenesis refers to the process by which new neurons are created. During development, this process occurs throughout the nervous system. In contrast, in the adult mammalian brain, genesis of new neurons has been reported across a wide range of mammalian species in only two regions: the dentate gyrus of the hippocampus and the subventricular zone-olfactory-bulb pathway. In the human brain, the preponderance of evidence indicates that there is very limited, if any, neurogenesis in the OB[14,22]. Interneurons may also be generated in other regions of the adult mammalian brain, including the striatum and forebrain.[23–25]. Following a stroke or other brain injury, neurogenesis may occur in other areas of the mammalian brain as well[26,27]. In contrast to mammals, in reptiles and birds, adult neurogenesis occurs in many regions of the adult brain[28–30]. Thus it appears that under normal conditions, as opposed to following a stroke or other brain trauma, greater brain complexity is associated with less widespread neurogenesis.

The process of neurogenesis begins with multi-potent neural progenitor cells or stem cells. These progenitor cells repeatedly undergo cell division and specialization into different cell types, some of which will be neurons. The entire process of neurogenesis includes this initial period of neural proliferation, followed by a period of pruning and maturation. Each of the young neurons either undergoes apoptosis (cell death) or survival and a prolonged period of maturation over the course of several weeks. A multitude of different factors promote one or both of these two components of neurogenesis: neuronal proliferation and survival.

Unique Properties of Immature Adult-Generated Neurons

The young, immature adult-generated neurons in the rodent dentate gyrus are affected very little by GABA inhibition, hence they fire more readily and are much more plastic than mature GCs, in spite of receiving fewer synaptic inputs[16,18,19,31–33] . By 4 weeks of age they are preferentially recruited into memory circuits[34]. As they mature further, they become more densely innervated by excitatory and inhibitory inputs; by age 6-8 weeks, they exert inhibitory control over other mature DG cells, and are themselves, in turn, regulated by feedback inhibition and fire very sparsely[33]. Similarly, in the olfactory bulb (OB), newly generated granule cells are preferentially recruited to encode novel odours[21]. The OB granule cells participate in a unique form of lateral dendro-dendritic synaptic interaction with OB mitral cells (the principal relay neurons), transforming discrete spatial input patterns into complex distributed temporal patterns[35]. This suggests that the OB granule cells, like the DG granule cells in the hippocampus, serve an important information-processing function. Thus, young adult-generated neurons in both the DG and OB are well positioned to be recruited selectively for new memory formation.

EVIDENCE OF A ROLE FOR NEUROGENESIS IN MEMORY

Does adult neurogenesis contribute significantly to behaviour? One way to address this question is to examine species that display natural variations in neurogenesis levels in the wild. For example, some species of birds exhibit seasonal changes in food-caching; their peak time of year for food caching and hence spatial learning, the autumn, coincides with a seasonal peak in neurogenesis levels[36]. Rodent species who cache winter food in a single site have much lower neurogenesis levels than species that cache at multiple sites[37]. Similarly, within-species geographical variations in food caching behaviour of red squirrels predict their neurogenesis levels [38]. Thus, in both birds and rodents, neurogenesis levels co-vary with spatial learning and memory demands.

Memory impairments after neurogenesis knockdown

What types of memory is neurogenesis important for? The hippocampus is well established to be critical for learning and retrieving complex associative memories, including memory for sequences, contexts, spatial layouts, and episodes[39–44]. Many studies have investigated whether some or all of these established hippocampal-dependent memory functions may rely, more specifically, upon neurogenesis. The most common protocol is to apply a knock-down method that interferes with cell proliferation, wait several weeks so that any remaining young neurons have fully matured, and then test learning and memory. Knockdown methods include anti-mitotic drugs, low-dose focal brain irradiation, and permanent or temporary genetic manipulations[45–48] . More ecologically valid manipulations include binge ethanol consumption[49], high fat diets[50], chemotherapy drugs[51], sleep deprivation[52], stress[53,54], contextual fear learning[55] and manipulation of adrenal hormones[7,56,57]. Further, there is an age-related decline in neurogenesis levels[58–60].

Different methods for knocking down neurogenesis, across different species, have yielded somewhat contradictory results. Nonethless, there is converging evidence from most (but not all) such studies

that neurogenesis knockdown disrupts performance on tasks that have a high interference component. One such task is contextual fear conditioning[46,48,61,62], where the animal has to associate a particular context with a subsequent aversive stimulus such as electric shock. Animals with intact neurogenesis levels exhibit a fear response specifically to the training context, whereas animals with low levels of neurogenesis will over-generalize their fear to different contexts, such as two different test boxes. Another potential source of interference in memory studies is a long time delay, whether the task involves a long delay between learning and the retention test, or the necessity to associate items across time. Importantly, animals with reduced neurogenesis exhibit memory deficits on long-term retention tests several weeks after learning in the Morris Water Maze (MWM) [48,63,64], associating stimuli across time delays (i.e. trace eyeblink conditioning)[45], and in delayed non-match to sample across long time delays[46]. Another type of interference arises in tasks that require discriminating between similar items within an environment. Neurogenesis knockdown disrupts performance on tasks that require discriminating between similar spatial locations or objects [65] (sometimes called behavioural tests of pattern separation, but see next section), as well as discriminating similar contexts[66–68]. Finally, a memory task can have interference due to overlapping but conflicting information being learned at different points in time. Animals with reduced neurogenesis are also vulnerable to this type of interference, showing deficts on tasks that create retroactive interference between current and previously learned information[69], proactive interference between overlapping stimulus sets learned at different times[70], and interference due to reversal learning[48,71–73] and extinction[74–76]. On the other hand, low interference versions of many of the above tasks are unaffected by a neurogenesis knockdown. Thus, neurogenesis is not required for initial acquisition in the MWM[48,63,64] or simple fear conditioning[46,61]. Similar findings on high interference olfactory tasks have been reported when OB neurogenesis is knocked down. Thus, in the OB, inhibition of postnatal neurogenesis impairs learning to discriminate highly overlapping odours, and long-term retention and reversal learning of olfactory associations, while leaving intact simple odour discrimination and odour associative learning.[77–80] Moreover, post-training ablation of adult-generated neurons impairs previously learned odor-reward associations, contextual fear conditioning, and memory for spatial locations and visual discriminations in the MWM [81,82]. Thus on tasks that may not require neurogenesis for acquisition, such as olfactory association learning, and spatial and non-spatial variants of the MWM, if the young neurons are recruited for memory formation, they will then be involved crucially in subsequent memory retrieval.

Positive effects of neurogenesis knock-down on memory

If knock-down of neurogenesis disrupts long-term memory, might it impart a *benefit* on tasks requiring short-term or working memory, when they are best performed by ignoring past memories? Saxe et al[83] created just such a task. In an 8-arm radial maze, rodents were required to remember which sequence of arms had been rewarded most recently, ignoring previously learned overlapping sequences. As predicted, rodents with reduced neurogenesis outperformed animals with intact neurogenesis levels on this task.

Memory enhancement after neurogenesis up-regulation

In addition to down-regulators, numerous extrinsic factors up-regulate neurogenesis. In the hippocampus, these include running[84], learning[85], environmental enrichment[86], dietary restriction[87] and dietary supplements that include anti-oxidant and anti-inflammatory factors[88–92]. These up-

regulators can act on neurogenesis via dissociable mechanisms; running mainly affects proliferation whereas learning and enrichment increase neuronal survival[93]. In the olfactory bulb, up-regulators of neurogenesis include exposure to olfactory enrichment and olfactory discrimination learning[94–97] but not exercise[98].

In contrast to the effects of anti-neurogenic factors, as one would expect, pro-neurogenic factors *promote* performance on high interference memory tests, including contextual fear conditioning[99], discriminating similar spatial locations[100], and discriminating similar contexts[67,101]. Moreover, pro-neurogenic factors such as running, environmental enrichment, and diet supplementation can mitigate the neurotoxic effects of alcohol exposure, stress, ageing, and irradiation on the brain and protect neurogenesis-dependent memory functions[70,102–105].

Memory impairment after neurogenesis up-regulation

Most studies that have investigated the functional effects of neurogenesis-upregulation have tested learning and memory after several weeks of an intervention such as exercise. Alternatively, one can up-regulate neurogenesis post-learning, to ask whether an increase in neurogenesis aids or interferes with memory retention. When adult rodents were exposed to wheel running after learning in a contextual fear conditioning task, this post-learning upregulation of neurogenesis was found to interfere with the previously acquired contextual fear conditioning response[106]. One interpretation of these results is that a basic function of neurogenesis, when levels are elevated, is to promote memory clearance (see the "Memory clearance hypothesis" discussed in the next section)[106]. As post-natal neurogenesis levels are highest in the infant brain, this also provides an explanation of infantile amnesia[106].

Converging evidence from human studies

Considering the importance of neurogenesis for memory in non-human animals, it is of great interest to know whether the same holds true in humans. In the absence of a non-invasive in vivo measure, all *direct* evidence of neurogenesis in the human adult brain comes from post-mortem assays[11–14]. Several imaging methods show promise for assaying biological indicators of neurogenesis *in vivo*. In rodents, aerobic exercise up-regulates both neurogenesis and angiogenesis in the DG; these changes in angiogenesis can be detected using contrast-enhanced MRI of DG blood volume and correlate with increased neurogenesis, while in humans, the same exercise-induced increase in DG blood volume is observed after several weeks of exercise. [107] Other promising methods for imaging neurogenesis indicators include MR spectroscopy[108] and PET[109], although current methods lack sufficient specificity [110].

Several investigators have developed human analogues of neurogenesis-dependent cognitive tests used in rodents. Extrinsic up- and down-regulators of neurogenesis in rodents should have similar impact on human performance. Consistent with this prediction, humans with symptoms of a first episode of depression were impaired on the CANTAB delayed match to sample task[111], which tests delayed recognition memory for images of abstract, complex objects amongst a set of highly overlapping lures. Elevated stress and depression scores also predict impairments on the Mnemonic Similarity Task (MST) and variants[112,113], which test memory for images of every day objects versus highly similar lures. Conversely, aerobic response to several weeks of exercise correlates with changes in performance in the MST[113]. Finally, those with elevated stress, depression and binge

alcohol scores are more impaired on tests of memory for overlapping spatial locations[114]. Thus, converging evidence across species suggests that hippocampal neurogenesis plays a similar role in human memory to that in rodents.

Common factors across neurogenesis-dependent tasks: Overcoming interference

The evidence reviewed above indicates that neurogenesis is required for many different memory tasks. These include distinguishing recently studied items from spatially or visually overlapping lures, learning distinct representations for items encountered in similar contexts, memory for items across long time delays, and extinguishing or reversing previously responses. The commonality across this wide range of seemingly disparate neurogenesis-dependent tasks is that they require memory representations that are robust against many different types of interference. In the next section, we consider alternative theoretical perspectives on the function of neurogenesis that attempt to account for these and other findings.

THEORETICAL PERSPECTIVES

Pattern separation

One of the most widely proposed functions of neurogenesis is to promote pattern separation. The term pattern separation was coined by computational modellers to refer to a type of neural coding, whereby overlapping input patterns are coded as less overlapping output codes. One way to achieve a less overlapping output code is via sparse coding, as illustrated in Figure 1a. Given that pattern separation is a characteristic of the neural code, pattern separation can only be verified by recording neural activation patterns. Nonetheless, many researchers use the term "behavioural pattern separation" to refer to almost any behavioural task that has a high interference component, assuming that a behavioural assay correlates with the underlying, hypothesized neural code.

Evidence of pattern separation in the dentate gyrus

While there is some empirical support for the role of the DG in pattern separation (in its original sense), the role of neurogenesis in this process remains controversial. Computational models of memory with sparse coding confirm that sparse coding leads to greater pattern separation, and that pattern separation is an effective mechanism for mitigating memory interference[115–118]. Given the extremely sparse firing rates of neurons in the DG[119], many modellers have adopted the assumption that pattern separation is a fundamental computational function of the DG, while pattern completion (cued memory retrieval) is a function of the CA3 region[115–118,120–122]. This charicature of a hippocampus that performs pattern separation in the DG and pattern completion in CA3 has become pervasive in the literature. However, like any charicature, it captures some key features, while ignoring many important details. Findings from electrophysiological and immediate early gene activation studies confirm that the DG robustly differentiates distinct contexts and environments, even based on very subtle features such as task demands, by recruiting different subsets of granule cells [119,123–126], consistent with sparse coding and pattern separation in the DG. Evidence from human fMRI studies lends further support to this notion[127]. Importantly, however, some of these activation studies also paint a more nuanced picture, as a large subset (about 30%) of granule cells are jointly recruited when an animal is exposed to two different contexts or environments, or even

the same environment under different task demands[123,125,128–130], a finding that is inconsistent with sparse coding and pattern separation. One possible explanation for these findings is that the subset of neurons activated across multiple contexts is the hyperactive, immature neuron population.

Does neurogenesis contribute to pattern separation?

The extensive evidence of a role for hippocampal neurogenesis in high interference behavioural tasks (which are often referred to as "behavioural pattern separation" tasks, a highly problematic term), led to the suggestion that neurogenesis could be directly responsible for pattern separation[131]. However, such a direct relation seems unlikely given that immature (4-6 week old) neurons are hyperactive rather than firing sparsely. Computational modellers have established that in neural models that have higher activity levels, there is a greater probability of overlap between neural codes for different memories, whereas in neural models that employ sparse codes, there is greater pattern separation (i.e. less pattern overlap).[132] Indeed, a recent model of the dentate gyrus demonstrates that the addition of highly active young neurons decreases sparse coding, decreases pattern separation, and yet improves memory performance.[133]

An updated view is that the young neurons may increase sparse coding, leading to increased pattern separation, in an indirect manner, by recruiting greater feedback inhibition onto mature granule cells[134–136]. The increased recruitment of feedback inhibition over mature granule cells is also consistent with the hypothesis of a circuit-level homeostatic mechanism that regulates overall activity within the DG[137]. Thus, high neurogenesis levels, translating into high activity levels in the immature granule cell population, require a compensatory lowering of activity levels in the mature cell population in order to balance overall activity in the DG.

Pattern integration and the memory resolution hypothesis

Given that the behaviour of the young immature neurons is inconsistent with the pattern separation hypothesis, how else might these neurons contribute to memory encoding? A very different idea is that the immature neurons, by firing continuously over time, may function as pattern integrators rather than pattern separators.[138–140] Thus, the immature neurons could provide the representation of temporal context that binds together elements of an episode. In support of this idea, electrophysiological recordings reveal distinct pools of DG neurons activated in different contexts that are well separated in time; either decreasing this temporal separation or knocking down neurogenesis attenuates their contextual selectivity, such that many of the young neurons fire in distinct but similar contexts.[141]

A more recent advancement on the above idea is the memory resolution hypothesis, which proposes complementary roles for the immature and mature neurons. The young immature neurons are coarsely tuned to a wide range of features, allowing them to better represent new information, while the mature neurons encode information at a high resolution, minimizing overlap between memory representations[142–144]. This account attributes the pattern separation function to the mature granule cells (enhanced by feedback inhibition from immature neurons), and the pattern integration function to immature neurons. However, this account has trouble explaining how highly similar items could be encoded within the same context. Given that mature granule cells are not very plastic relative to immature neurons, and tightly tuned to contexts that were learned,

presumably, when they were at an immature stage, how could they be recruited to differentiate novel, similar features?

The Memory clearance hypothesis

Rather than promoting memory formation, a rather different role has been proposed for newly generated neurons in memory clearance.[137,145–149] This could be a means by which the brain clears out older, more remote memories in favour of novel memory encoding. Such a role in memory clearance is not necessarily incompatible with a dual role for neurogenesis in supporting novel memory formation. There are several lines of empirical support for the memory clearance hypothesis. For example, mice with elevated levels of neurogenesis exhibit compromised memory stability.[150] Importantly, the memory clearance hypothesis also provides a compelling explanation of infantile amnesia[149], as neurogenesis levels in mammalian hippocampi are highest at birth, and decline with age. On the other hand, the memory clearance hypothesis is difficult to reconcile with direct evidence from rodents,[69] and indirect evidence from humans,[151] that higher neurogenesis levels protect remote memories from retroactive interference with newly acquired information. Given the support for both of these theories, interference reduction versus memory clearance, an important avenue for futher research is to discover how these apparently contradictory lines of evidence can be reconciled.

CONTROVERSIES

Could young neurons decrease pattern separation while decreasing interference?

One issue that is difficult to explain for the theories described so far is that young neurons seem to *decrease* pattern separation, and yet they are crucial for mitigating interference. The evidence reviewed above indicates that the young neurons are required for a wide range of high interference tasks, whether the interference arises between similar stimuli in the same context, or similar events in different contexts separated in time. Importantly, while neurogenesis levels decline with age, pattern separation increases with age, as measured by activation patterns in the DG using immediate early gene labelling[128]. Moreover, animals' ability to discriminate two contexts is positively predicted by the overlap: overlapping representations are associated with improved discrimination[128].

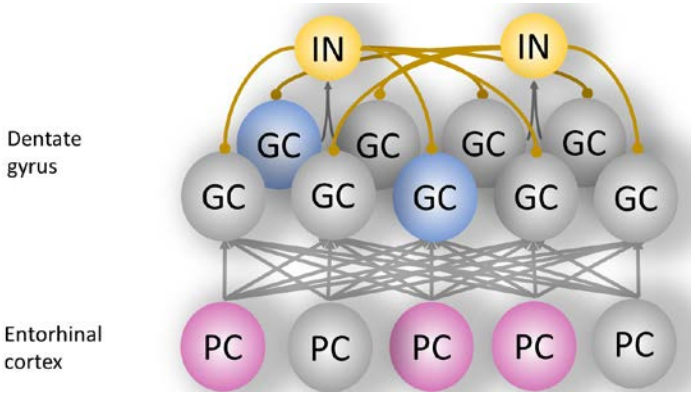
Sparse connectivity decreases interference

Sparse coding / pattern separation is not the only strategy for overcoming interference. In fact, under conditions of very high plasticity, it does not solve the problem. Computer simulations of "Competitive Learning" neural networks[152–154], with ultra-sparse coding enforced via a winner-take-all activation function, require very slow adjustment to the synaptic weights, and many iterations through a set of training patterns (as opposed to one-shot learning), for proper functioning. Otherwise, they suffer from interference with previous learning, illustrating the stability-plasticity tradeoff[154].

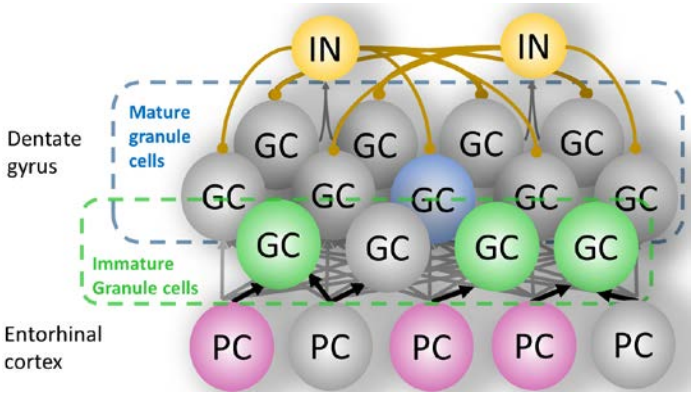
One strategy for overcoming interference, while maintaining high levels of plasticity, is to have sparse connectivity. This seems to be the strategy used by the young immature neurons. They are

very sparsely connected, receiving relatively few inputs from the entorhinal cortex, and few if any inputs from lateral neighbors or descending inputs from CA3 neurons; if they survive and mature, they undergo experience-dependent synaptic remodelling, becoming increasingly innervated by cortical and hippocampal inputs[155]. As illustrated in Figure 1b) and c), a pool of young, sparsely connected, immature granule cells can respond to two different overlapping stimuli with overlapping and yet distinct patterns of activation. The sparse connectivity of the immature granule cells increases the tendency for each neuron to respond to a different subset of input features. Recent empirical evidence supports the notion that the low synaptic connectivity of immature neurons prevents them from firing broadly to a wide range of stimuli. [156] Computer simulations of a model with these characteristics lend further support to the proposal that immature neurons with high plasticity and sparse connectivity are able to overcome interference, while simultaneously *decreasing* pattern separation[133].

A



B



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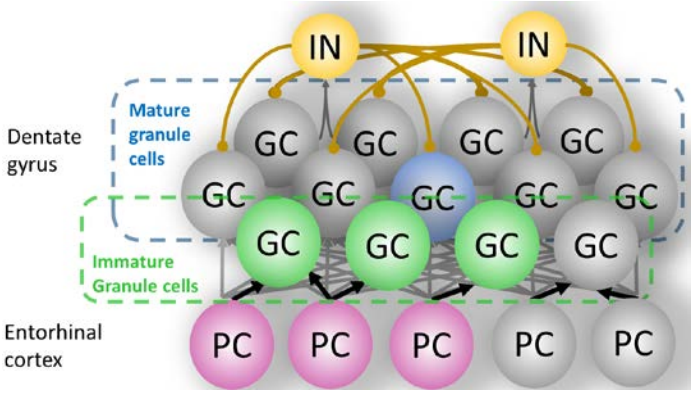

Figure 1. Schematic models of the hippocampus, using sparse coding (A) versus neurogenesis and sparse connectivity (B, C) to overcome interference. Model input is a distributed pattern of activation across the entorhinal cortex pyramidal cells (PC; activated cells shown in pink). This input generates a sparse pattern of activation across the mature dentate granule cells (GCs; active cells shown in blue). PCs are densely interconnected to mature GCs, which are themselves interconnected via inhibitory interneurons (IN, shown in yellow). In B) and C), the model with neurogenesis also includes immature GCs (active cells shown in green); entorhinal PCs are sparsely connected to the immature GCs. The model shown in B) and C) is presented with two different input patterns and in response, generates identical sparse activation patterns in mature GCs, and overlapping but distinct distributed activation in immature GCs. While the two input patterns overlap by 40%, the two patterns of activation in the immature GC overlap by 50%, hence a decrease in pattern separation. The model is nonetheless capable of maintaining distinct neural codes for the two similar inputs, in spite of high plasticity in the immature cell population, due to the sparse connectivity of the immature GCs.

Another potential strategy for overcoming interference, while maintaining high levels of plasticity, is to use top-down expectations from descending pathways to compute a novelty / mismatch signal, and have the mismatch signal drive recruitment of new neurons for encoding new memories. Such a mechanism was proposed several decades ago in a model of classification learning known as Adaptive Resonance Theory[154,157]. Computational models of mismatch detection within the DG-CA3 circuit[122,158], together with feedback projections from the CA3 to DG, could explain how novelty/ mismatch signals might drive DG circuit dynamics, inhibitory feedback and plasticity. Such a mechanism could allow the circuit to operate in two distinct modes, memory storage versus recall.

The fate of old neurons and old memories

A major unresolved issue is what happens to adult-born neurons as they continue to age. Evidence suggests that adult-generated neurons recruited during memory acquisition are also recruited for subsequent memory retrieval[159]. However, behaviourally, it is virtually impossible to distinguish memory formation from memory retrieval, as memories may be modified whenever they are retrieved. Indeed, the recruitment of young immature neurons has been implicated in this process of memory reconsolidation[160].

Evidence from neurogenesis knockdown studies suggests an important role for neurogenesis in long-term retention and remote memory[48,63,64], also supported by correlative evidence in humans[151]. On the other hand, it has been found that as the mature granule cells age, they become less and less active, and eventually may retire into silence[130]. It would be surprising if this was the fate of all adult-generated neurons, but this is an unresolved issue.

The neurogenic theory of depression

The intriguing link between stress, depression and neurogenesis led to the neurogenic theory of depression[161]. According to this view, reduced neurogenesis causes depression, and restoration of neurogenesis leads to the recovery from depression. In support of this view, stress is well established to reduce neurogenesis[162], it is widely believed to play a major role in causing depression, and is the basis of all animal models of depression. Further, many anti-depressant factors, including SSR's, ECT, aerobic exercise, and successful stress coping, up-regulate neurogenesis in animal models[84,163–168]. What remains a matter of debate is whether neurogenesis plays a causal role in either the pathogenesis of depression or in its recovery. Suppressed neurogenesis by itself does not cause a depressive or anxious phenotype, leading to the suggestion that it is not directly involved in mood regulation, but instead modulates emotional responding via its role in mnemonic processing[169]. On the other hand, in rodent models, neurogenesis knockdown increases the HPA axis response[170] and predisposes the animal to be more sensitive to the effects of stress[171], while neurogenesis knockdown blocks the anti-depressant effects of SSRIs[172,173].

Conclusion

While empirical studies point to a role for neurogenesis in reducing interference between similar events in memory, the mechanism by which this interference reduction is achieved is still under debate. Earlier theories postulated a role for the young neurons in pattern separation, a mechanism by which similar neural activation patterns are encoded as very sparse, less overlapping representations. However, the immature neurons do not behave in a manner consistent with the proposed pattern separation function. The evidence reviewed above indicates that these neurons fire at low thresholds, generating highly overlapping neural codes for similar events, and yet, they are crucial for distinguishing similar events or contexts. An alternative view is that the young neurons generate distributed codes across similar contexts that are overlapping, but nonetheless distinct, by using sparse connectivity. Their sparse perforant path afferent connections cause the immature neurons to maintain some degree of selectivity in spite of very high plasticity levels. Additionally, top-down mismatch signals from the CA3 region could play a role in regulating activity and plasticity levels in the DG, and gating the operation of the circuit between storage and recall modes. For such a scheme to work, the top-down mismatch signal would have to gate the recruitment of immature DG neurons for novel memory encoding. While this general scheme is intriguing, it remains to be worked out how such a function could operate within the DG / CA3 circuit, and for such a model to be validated empirically.

An important future application of neurogenesis research is in the treatment of stress-related neuropsychiatric disorders. While a causal link between neurogenesis and depression has yet to be established, an emerging view is that animals with reduced neurogenesis have an impairment at

encoding and recognizing contexts, resulting in an over-generalization of fear and an increased vulnerability to mood disorders. [174] Conversely, rescue of neurogenesis may support the normal hippocampal role in exerting contextual modulation over neural circuits subserving stress, emotion and other responses.[175,176]

Neurogenesis research also has important implications for treating age-related neuropathology. Factors associated with age-related neurodegeneration and dementia, including a dysregulated HPA axis, chronic inflammation, and microglial activation, also impair neurogenesis[60,91,177–179]. Thus, a promising target for interventions in this wide range of disorders is to up-regulate neurogenesis levels and associated neurotrophic factors. Increasing neurogenesis and neurotrophic factor levels via exercise, diet, and environmental enrichment may impart neuroprotection against stress, ageing and dementia[104,180–184]. Also, there may be important interactions amongst these factors in promoting optimal learning[185,186] and a healthy brain[104,187].

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Figure captions

Figure 1. Schematic models of the hippocampus, using sparse coding (A) versus neurogenesis and sparse connectivity (B, C) to overcome interference. Model input is a distributed pattern of activation

across the entorhinal cortex pyramidal cells (PC; activated cells shown in pink). This input generates a sparse pattern of activation across the mature dentate granule cells (GCs; active cells shown in blue). PCs are densely interconnected to mature GCs, which are themselves interconnected via inhibitory interneurons (IN, shown in yellow). In B) and C), the model with neurogenesis also includes immature GCs (active cells shown in green); entorhinal PCs are sparsely connected to the immature GCs. The model shown in B) and C) is presented with two different input patterns and in response, generates identical sparse activation patterns in mature GCs, and overlapping but distinct distributed activation in immature GCs. While the two input patterns overlap by 40%, the two patterns of activation in the immature GC overlap by 50%, hence a decrease in pattern separation. The model is nonetheless capable of maintaining distinct neural codes for the two similar inputs, in spite of high plasticity in the immature cell population, due to the sparse connectivity of the immature GCs.

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