Neuron
Perspective: Point/Counterpoint

Here, we present two paired Perspectives that explore alternative viewpoints on the roles of adult-born neurons. In these Point/Counterpoint pieces, René Hen and colleagues and Rusty Gage and colleagues present their views on the potential functions of adult neurogenesis and how new neurons contribute to cognition and behavior. We hope that these paired Perspectives will be informative and will stimulate discussion in the field.

Pattern Separation: A Common Function for New Neurons in Hippocampus and Olfactory Bulb

Amar Sahay,[1,2] Donald A. Wilson,[3] and René Hen[1,2,*]
[1]Departments of Neuroscience and Psychiatry, Columbia University, New York, NY 10032, USA
[2]Division of Integrative Neuroscience, The New York State Psychiatric Institute, New York, NY 10032, USA
[3]Emotional Brain Institute, Nathan Kline Institute for Psychiatric Research, and Child and Adolescent Psychiatry, New York University School of Medicine, Orangeburg, New York, NY 10962, USA
*Correspondence: rh95@columbia.edu
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While adult-born neurons in the olfactory bulb (OB) and the dentate gyrus (DG) subregion of the hippocampus have fundamentally different properties, they may have more in common than meets the eye. Here, we propose that new granule cells in the OB and DG may function as modulators of principal neurons to influence pattern separation and that adult neurogenesis constitutes an adaptive mechanism to optimally encode contextual or olfactory information. See the related Perspective from Aimone, Deng, and Gage, "Resolving New Memories: A Critical Look at the Dentate Gyrus, Adult Neurogenesis, and Pattern Separation," in this issue of *Neuron*.

Introduction

Making sense of our external world requires us to continuously assess if our day-to-day experiences are different or similar to those previously encountered. In this way, we can differentiate today's car parking location from that of yesterday and two beach vacations from one another. Conversely, we may vividly remember a beach vacation when we see palm trees or recall a traumatic bicycle accident when we see a bicycle on a street. The balance between keeping similar episodes separate while retrieving previous memories based on environmental cues is thought to require two opposing processes, pattern separation and pattern completion. Pattern separation is defined as the process by which overlapping or similar inputs (representations) are transformed into less similar outputs whereas pattern completion is the reconstruction of complete stored representations from partial inputs that are part of the stored representation (Colgin et al., 2008; Wilson, 2009). Understanding how neural circuits within the hippocampus and the olfactory system subserve these processes has received considerable attention in this last decade.

Experimental evidence for a role of the DG in pattern separation first came from lesion studies in rodents showing that ablation of the DG impaired discrimination of two spatial locations based on distal environmental cues (Gilbert et al., 2001). More recent studies relying on genetic approaches to specifically manipulate DG functions have yielded similar results (McHugh et al., 2007). Collectively, these studies suggest that the DG is required to minimize interference between overlapping spatial or contextual information (Figure 1). Multitetrode recordings of hippocampal ensemble activity have begun to identify the neuronal correlates of pattern separation in the DG. Subtle morphing of a rat's environment is sufficient to elicit remapping of firing rates of place cells in the DG suggesting that small changes in spatial input can produce highly divergent output (Leutgeb et al., 2007). However, multitetrode recordings do not capture the activity of the entire DG neuronal population and circuit based genetic approaches that permit visualization and manipulation of neuronal activity at a population level along the entire DG will prove invaluable. Neurocognitive testing and fMRI studies in humans have also suggested a role for the DG in pattern separation (Bakker et al., 2008; Lacy et al., 2010).

Like the hippocampus, the olfactory system deals with complex spatial and temporal patterns (Figure 1). Both individual molecules and complex molecular mixtures can evoke highly overlapping spatial patterns within the OB and separation of these patterns is required for high acuity odor discrimination. Using analysis of ensemble single-unit activity, Wilson and colleagues (Barnes et al., 2008; Wilson, 2009) have demonstrated an apparent segregation of pattern recognition functions between the olfactory bulb and anterior piriform cortex (PC), remarkably similar to that described for contextual pattern recognition in DG and hippocampal area CA3 (Leutgeb et al., 2007). As in most other sensory systems, olfactory perceptual acuity is experience-dependent. Humans (Rabin, 1988) and other animals (Cleland et al., 2002; Fletcher and Wilson, 2002) can improve discrimination of molecularly similar odorants through training, and this perceptual learning appears to modulate pattern separation within olfactory bulb local circuits.

Neurogenesis Modulates Pattern Separation in the Dentate Gyrus and Olfactory Bulb

The continuous modification of circuitry of the DG and the OB by integration of new neurons suggests that adult-born neurons may

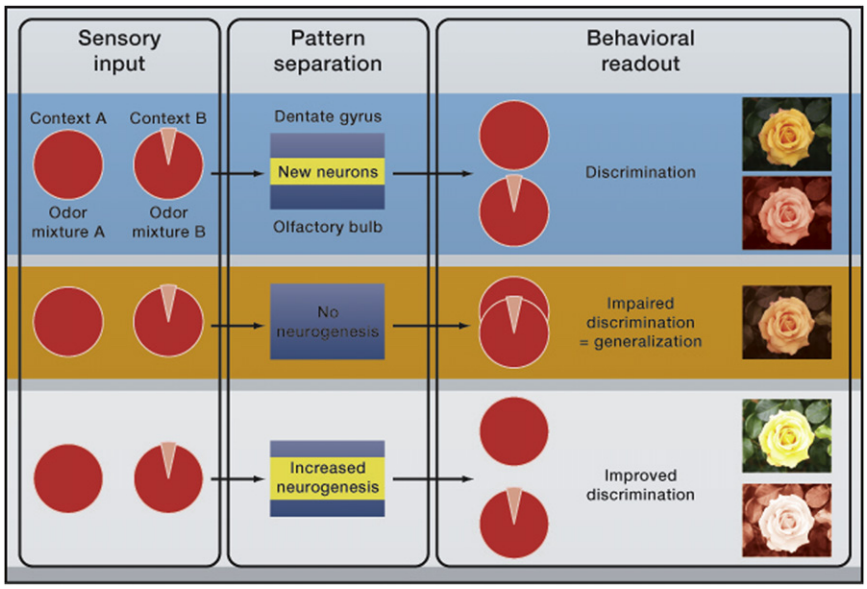

Figure 1. Neurogenesis and Pattern Separation in the Dentate Gyrus and Olfactory Bulb

The dentate gyrus and the olfactory bulb (blue boxes) are required for discrimination between similar contexts and similar odors (A and B), respectively. This process is termed pattern separation and is modulated by adult neurogenesis which is the generation of new neurons throughout life (yellow box). When adult neurogenesis is blocked either by irradiation (X-ray) or by genetic ablation, discrimination is impaired leading to generalization and an inability to distinguish A from B. In contrast when neurogenesis is stimulated by genetic manipulations (iBax) or exercise, discrimination is enhanced.

functionally contribute to these two regions. Since both of these populations of adult-born neurons exhibit critical periods of plasticity during a specific window of their maturation, it is unlikely that adult neurogenesis simply adds new equivalent units but instead expands the capacity for plasticity in the DG and OB. Here, we review growing evidence suggesting that new neurons in both the DG and OB contribute to pattern separation.

Dentate Gyrus

Although the general pattern of afferent and efferent connectivity of new neurons in the DG recapitulates that of developmentally generated dentate granule neurons, new neurons exhibit distinct physiological properties relative to mature neurons during a specific window of their maturation. Specifically, young 4-8-week-old adult-born neurons show greater synaptic plasticity and, increased excitability (see Ming and Song, 2011, this issue of *Neuron*). These features of young adult-born neurons may be critical for their recently discovered role in pattern separation (Figure 1).

Clelland and colleagues used a two-choice touch screen spatial discrimination task and a delayed nonmatching to place radial arm maze task to first demonstrate the impact of blocking hippocampal neurogenesis on spatial pattern separation (Clelland et al., 2009). In both tests, the correct choice that mice were required to make relied on discrimination of small or large spatial separations. Consistent with previous studies using DG lesions, the authors found that blockade of adult hippocampal neurogenesis by hippocampal x-irradiation impaired the animal's ability to make fine, but not large, spatial discriminations. More recently, Sahay and colleagues used a contextual fear discrimination learning task, previously shown to require pattern separation in DG, to test whether new neurons are required for distinguishing between similar contextual representations (Sahay et al., 2011). The authors found that hippocampal x-irradiated mice exhibited similar levels of freezing behavior in both the shock associated training context and a similar no-shock "safe" context, unlike controls that learned to discriminate between the two contexts (X-ray; Figure 1). A second study using the same contextual fear discrimination learning task yielded analogous results (Tronel et al., 2010). Together, these studies show that new neurons are required for pattern separation in three different DG dependent behavioral paradigms and raise the possibility that increasing adult hippocampal neurogenesis may enhance pattern separation. To directly address this possibility, Sahay and colleagues developed a genetic strategy to selectively increase adult neurogenesis (Sahay et al., 2011). In the contextual fear discrimination learning task, mice with more functionally integrated adult-born dentate granule neurons (iBax mice; Figure 1) were better at distinguishing between two similar contexts. These results indicate that increasing adult hippocampal neurogenesis is sufficient to improve pattern separation.

Although behavioral assays that explicitly measure pattern separation have been critical in establishing the link between new neurons and pattern separation, behavioral paradigms which test memory interference have also proven invaluable. For example, tests of spatial relational memory requiring an animal to disambiguate overlapping room cues to find a hidden platform necessitate recruitment of the dentate gyrus. Recent studies showing a role for adult-born neurons in such tasks are consistent with the idea that neurogenesis contributes to pattern separation (Dupret et al., 2008; Garthe et al., 2009; Wojtowicz et al., 2008).

The convergence of these loss-of-function and gain-of-function studies causally linking bidirectional changes in levels of adult hippocampal neurogenesis with pattern separation efficiency bolsters the hypothesis that the unique properties of young adult-born neurons are instrumental to their functions. How do a relatively small number of highly plastic young adult-born neurons influence pattern separation? Efforts to address this question are underway, and there are currently two distinct but non-mutually exclusive hypotheses. The first model emphasizes a cell autonomous function for new neurons as individual encoding units (Aimone et al., 2010). The new neurons may be the preferred substrate for place cell remapping in response to subtle changes in the animal's environment. Through their mossy fibers, new neurons may also influence place cell remapping in CA3. To begin to address this possibility, we need to

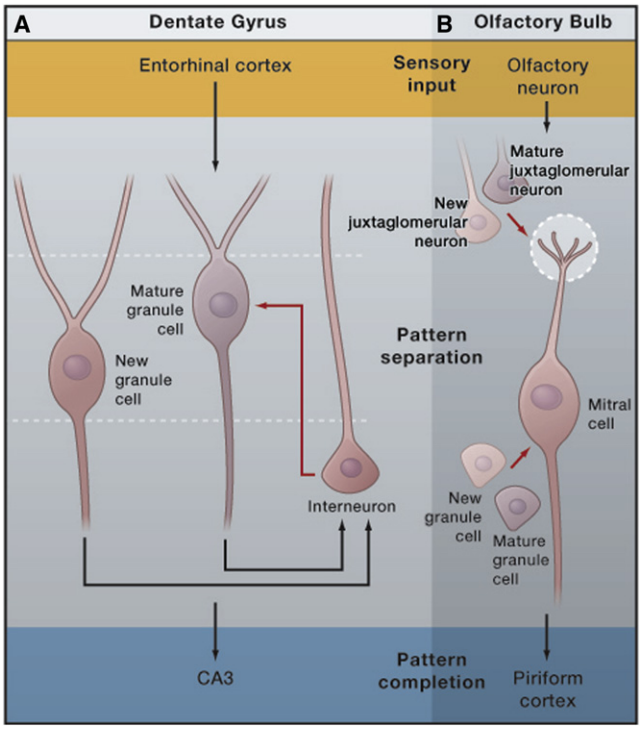

Figure 2. Neural Circuits Underlying Pattern Separation in the Dentate Gyrus and Olfactory Bulb

(A) Dentate Gyrus. Contextual information arrives in the dentate gyrus from the entorhinal cortex via the perforant path. In the dentate gyrus, the granule cell layer (space between the dotted lines) is composed of mature granule cells born during development and new granule cells born in adulthood. Both mature and new granule cells activate a variety of interneurons, such as basket cells, and excitatory neurons such as mossy cells (not shown). Mossy cells send axons to the molecular layer where they activate both inhibitory interneurons and excitatory granule cells. Interneurons, in turn, inhibit mature granule cells but not new granule cells (at least when they are less than 4 weeks old). Activation of new granule cells may therefore result in a preferential inhibition of mature granule cells and consequently, increase sparseness of activity in the dentate gyrus, which may improve pattern separation.

(B) Olfactory Bulb. Sensory information arrives in the olfactory bulb through axons of olfactory sensory neurons, which synapse onto dendrites of principal cells (mitral or tufted cells) in a structure called a glomerulus (dashed circle). A variety of inhibitory interneurons inhibit the mitral or tufted cell either at the level of the glomeruli (mature juxtaglomerular neuron) or at dendrodendritic synapses (mature granule cell). Adult neurogenesis generates new granule cells and new juxtaglomerular neurons, which also inhibit mitral/tufted cells. In addition, adult-born granule cells contact other granule and juxtaglomerular cells (not shown here). Like in the dentate gyrus, the addition of new neurons in the olfactory bulb may therefore result in increased inhibition and possibly as a result, increased pattern separation.

Pattern completion has been proposed to take place in the projection zones of the dentate gyrus and olfactory bulb, which are the hippocampal CA3 field for contextual information and the piriform cortex for olfactory information.

Black arrows, excitatory projections; red arrows, inhibitory projections.

know how dentate granule place cell properties or mossy fiber-CA3 pyramidal neuron synapse maturation track with the development of adult-born neurons. Ensemble recordings from behaving mice in which adult neurogenesis has been bidirectionally manipulated will provide insight into how adult-born neurons sculpt place cell dynamics in DG and CA3.

The second model proposes a modulatory role for young-adult-born neurons and is predicated upon the lower threshold for firing of young adult-born neurons, their insensitivity to GABAergic inhibition, and their connections with interneurons and mossy cells in the DG hilar microcircuit (Figure 2; Sahay and Hen, 2007; Lacefield et al., 2010; see also Doetsch and Hen, 2005; Ming and Song, 2011). Within this framework, young adult-born neurons preferentially respond to subtle changes in context (weak inputs) because of their lower threshold of activation and influence the firing probability of mature dentate granule neurons through feedback inhibition conveyed either directly by local inhibitory interneurons or indirectly via mossy cells. Since mossy cells also form monosynaptic excitatory contacts onto dentate granule neurons, the summation of feedback inhibition and excitation relative to the strength of perforant path inputs will dictate the degree of sparseness of activity in the DG and consequently, pattern separation efficiency (Rolls, 2010). Moreover, neurogenesis-dependent feedback inhibition may also enhance the divergence between given overlapping inputs into the DG and corresponding outputs. In addition, through recruitment of interneurons whose dendrites and axons ramify in the molecular layers of the DG, new neurons may directly modulate afferent inputs and dendritic excitability. Preliminary support for a modulatory or non-cell-autonomous function for new neurons comes from a study showing that ablation of adult-born hippocampal neurons results in an increase in gamma oscillatory activity suggestive of increased coordinated network activity in the DG (Lacefield et al., 2010). A second study found a reduction in inhibitory inputs to the DG following ablation of adult-born neurons (Singer et al., 2011). Analysis of mature granule cell activity and levels of inhibition in the DG of mice in which adult neurogenesis levels are manipulated is required to demonstrate that new neurons modulate the activity of mature granule cells to influence pattern separation.

In addition to these proposed active roles for new neurons in pattern separation, neurogenesis may also influence encoding in other ways. For instance, the competition between new and old neurons for perforant path inputs (Toni et al., 2007) and potential postsynaptic targets may result in a redistribution of synaptic weights. Furthermore, a recent study showed that varying levels of neurogenesis dictated the temporal extent of hippocampal dependence of memories (Kitamura et al., 2009). Thus, neurogenesis may ensure that an appropriate amount of space is available in the DG for encoding information by transferring memories out of the DG to the neocortex.

Olfactory Bulb

Odor acuity is in part dependent on pattern separation in the olfactory bulb, and olfactory bulb pattern separation is modulated by, and dependent on, local inhibitory interneurons, many of which are generated in adulthood. There are two populations of adult generated interneurons in the olfactory bulb, juxtaglomerular neurons (periglomerular and short axon cells) and inhibitory granule cells (Lazarini and Lledo, 2011), that contribute to lateral inhibition and the spatiotemporal structure of olfactory bulb output activity. This inhibition helps enhance contrast between similar inputs (Luo and Katz, 2001; Schoppa and Urban, 2003; Yokoi et al., 1995) and thus enhances separation between similar patterns of olfactory sensory neuron input (Figure 2).

Prolonged odor exposure and odor conditioning not only induce a memory for the experienced odor, but also enhance

acuity for that odor relative to other similar odors. This memory and enhanced olfactory acuity are associated with modified newborn granule cell survival (Moreno et al., 2009; Rochefort et al., 2002; Rochefort and Lledo, 2005). In fact, given the spatial organization of odor-evoked activity across the olfactory bulb, cell survival is also spatially selective, with cells surviving primarily in the region activated by the exposure odor (Mandairon and Linster, 2009). In contrast, olfactory deprivation, which can impair pattern separation in the olfactory bulb (Wilson and Sullivan, 1995), reduces survival of adult generated granule cells (Mandairon and Linster, 2009)(Yamaguchi and Mori, 2005).

Reduced olfactory bulb neurogenesis disrupts normal synaptic inhibition and stimulus evoked gamma frequency oscillations (Breton-Provencher et al., 2009), which should impair odor-evoked activity patterns. Furthermore, as in the DG, young granule cells show more robust synaptic plasticity than mature granule cells (Nissant et al., 2009), and young granule cells are more responsive to novel odors (Mandairon and Linster, 2009). Interestingly, adult-born cells synapse on to all major cell types in the OB (Bardy et al., 2010; Carleton et al., 2003; Panzanelli et al., 2009). Thus, this pool of neurons may be particularly effective at shaping responses to novel odors in a manner which enhances pattern separation. Therefore, it is surprising that unlike manipulations of developmental bulbar neurogenesis (Bath et al., 2008; Gheusi et al., 2000), most manipulations of adult neurogenesis (Breton-Provencher et al., 2009; Imayoshi et al., 2008; Lazarini et al., 2009; Valley et al., 2009) have not found impairments in olfactory discrimination. However, two studies have shown a role for adult-born granule cells in olfactory discrimination (Moreno et al., 2009; Mouret et al., 2009). These discordant findings could be due to compensatory effects following chronic blockade of adult neurogenesis, underscoring the need to acutely manipulate adult-born neurons. Alternatively, it is possible that a role for adult-born granule cells in pattern separation is uncovered only in the most difficult tasks used to probe olfactory discrimination (Moreno et al., 2009). Indeed, blockade of neurogenesis does not impair discrimination of perceptually or molecularly distinct odors where pattern separation may be less critical (Breton-Provencher et al., 2009). A similar situation is seen in the DG where the impact of neurogenesis is most likely to be uncovered with increased task difficulty (Drew et al., 2010).

Neurogenesis as Adaptation to the Environment

Experience-dependent plasticity is a common feature of most central circuits, yet is most commonly mediated by changes in synaptic strength, membrane excitability or remodeling of synaptic or dendritic structure. These kinds of changes can be rapidly induced (seconds to hours) and rapidly reversed. Using neurogenesis to track and record experience, in contrast, functions on a timescale of weeks, suggesting that neurogenesis-based circuit changes may be most relevant for reflecting long-term, adaptive responses to the changing environment.

Dentate Gyrus

The exquisite regulation of adult hippocampal neurogenesis by environmental factors has been well documented (see Ming and Song, 2011, for a review), but how environmentally induced changes in levels of neurogenesis functionally relate to the organism is much less understood. Here, we propose that changing levels of neurogenesis constitute a long-term adaptive response to different environments by shifting the balance between pattern separation and pattern completion (Figure 3). For example, enriched environments are generally thought to promote exploration and learning and may exert greater cognitive demands by requiring encoding of details and generation and maintenance of multiple nonoverlapping representations. Increased levels of adult neurogenesis following environmental enrichment may serve two adaptive functions. First, it may facilitate the faithful processing of the complex environment through enhanced pattern separation thereby also ensuring rapid recognition of such environments in the future (Kempermann, 2008). Second, it may prevent the DG from being overburdened with contextual information by rapidly transferring memories out to the cortex (Kitamura et al., 2009). In contrast, decreased neurogenesis due to stressful environments may lead to generalization of individual features and enable the organism to avoid similar situations by restraining exploration. For example, increased generalization in a hostile environment may be adaptive because it promotes avoidance of most potential threats. It should be emphasized that changes in neurogenesis are not required for acute responses to the environment for which other synaptic modifications in the DG may suffice. Instead, environment-dependent changes in neurogenesis may prepare the organism for novel habitats on longer time scales.

Disruption in these normal adaptive regulations of neurogenesis may occur in pathological contexts resulting in excessive or impaired pattern separation (Figure 3). Excessive pattern separation may impede normal integration of environmental information, as the individual will devote too much attention to individual contextual and sensory features at the detriment of the "big picture." Behaviorally, this may manifest as cognitive inflexibility, increased preoccupation with minutiae, and unrestrained fixation on fine details as seen in autism spectrum disorders (Mottron et al., 2006; Soulières et al., 2009) or obsessive-compulsive personality disorder (American Psychiatric Association, 2000). In contrast, impaired pattern separation may lead to excessive generalization, which would cause an organism to lump multiple contexts or items together even if the similarity between them is minimal. Such a maladaptive response may underlie the increased generalization of new "innocuous" experiences with previously encountered aversive events seen in individuals with panic disorder (Lissek et al., 2010) and post-traumatic stress disorder (PTSD) (Peri et al., 2000). For example, in somebody who developed PTSD as a result of 9/11, the simple sight of a plane flying over New York City may be sufficient to trigger a panic attack. In addition, impaired pattern separation has also been reported during aging and in individuals with mild cognitive impairment (Toner et al., 2009; Yassa et al., 2010a, 2010b). Finally, perturbed interpretation of ambiguous cues when combined with a negative response bias may be a predisposing factor in depression (Beck, 2008; Becker and Wojtowicz, 2007; Enkel et al., 2010) and overgeneralized autobiographical memory is often associated with depression and PTSD (Sumner et al., 2010). Deficits in pattern separation may therefore represent a circuit-based endophenotype for these different disorders.

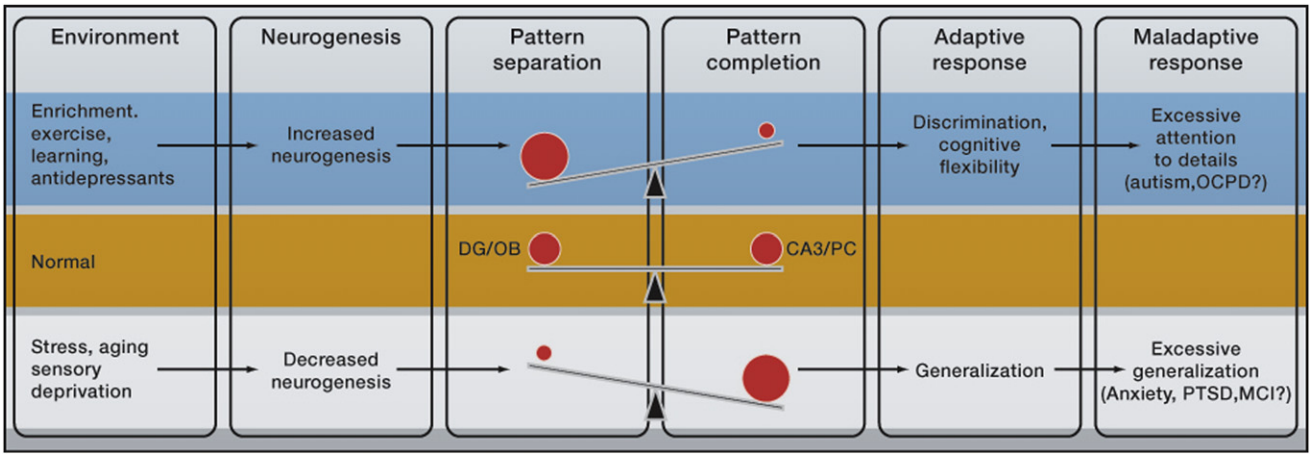

Figure 3. Environmental Influences on Neurogenesis and Pattern Separation

Environments rich in odors or contexts stimulate neurogenesis in the olfactory bulb (OB) and dentate gyrus (DG), respectively. Similarly, learning stimulates neurogenesis in the OB and DG depending on whether the modalities are olfactory or contextual and spatial. Other manipulations such as exercise or antidepressants stimulate neurogenesis primarily in the DG. Stress, aging, and sensory deprivation result in a decrease in neurogenesis in both the DG and OB. We propose that an increase in neurogenesis favors pattern separation, which alters the balance that normally exists between pattern separation (taking place in DG or OB) and pattern completion (taking place in CA3 or PC). Conversely, a decrease in neurogenesis impairs pattern separation, which shifts the balance in favor of pattern completion and results in generalization. These shifts may be a part of the normal adaptive response to changing environments. In an enriched environment, discrimination and cognitive flexibility (which result from increased pattern separation) are advantageous because they favor exploration and learning; in contrast, in a dangerous environment, generalization (which results from decreased pattern separation) may be advantageous because it favors avoidance of new and potentially dangerous situations. However, these normal adaptive responses when exaggerated may lead to pathologies: excessive generalization may for example lead to anxiety disorders such as post-traumatic stress disorder (PTSD) or to the impairments that often accompany aging such as mild cognitive impairment (MCI). Similarly, excessive pattern separation may lead to an excessive attention to details such as seen in some psychiatric disorders such as autism and obsessive-compulsive personality disorder (OCPD).

The finding that increasing adult hippocampal neurogenesis is sufficient to improve pattern separation suggests that neurogenesis may be harnessed to treat disorders with pattern separation deficits (Sahay et al., 2011) Interestingly, naturalistic interventions such as voluntary exercise have been shown to improve pattern separation in rodents (Creer et al., 2010). It is possible that increased adult hippocampal neurogenesis mediates some of the beneficial effects of exercise on pattern separation. Chronic antidepressant treatments, which are known to stimulate adult hippocampal neurogenesis, may also exert some of their behavioral effects through enhancing pattern separation; however this is yet to be demonstrated. Unraveling the molecular mechanisms underlying the plasticity of neural stem cells and adult-born neurons and identification of proneurogenic small molecules (Pieper et al., 2010; Wurdak et al., 2010) will catalyze the development of novel strategies to treat pattern separation deficits.

Olfactory Bulb

Olfaction is at the heart of mammalian life, playing critical and often necessary roles in mother-infant attachment, kin recognition, mate selection and recognition, food selection, predator avoidance, and homing. Each of these basic functions can include prolonged changes in internal state and the external chemical environment and often require remarkably precise separation of highly overlapping odorant stimulus patterns. Enhanced survival of newly generated olfactory bulb interneurons due to a springtime eruption of novel environmental odors could coincide with the need for enhanced pattern separation and the perceptual acuity necessary for navigating this rich olfactory world. In fact, prolonged enrichment of the odor environment enhances the survival (Rochefort et al., 2002) of adult-generated olfactory bulb interneurons and odor perceptual learning and memory (Mandairon and Linster, 2009). Together, these findings suggest that adult neurogenesis in the OB, as in the DG, may provide a mechanism for adapting to relatively stable changes in the environment, allowing for shifts in olfactory pattern separation and ultimately olfactory acuity.

Perturbed experience dependent regulation of olfactory bulb neurogenesis may result in unlimited pattern separation, which could come at the expense of pattern completion and perceptual stability. Given the ephemeral nature of odors, excessive pattern separation could lead to an overrepresentation of feature representation in slightly shifting stimuli, with each successive presentation of even the same stimulus being perceived as unique. Abnormal prominence of unique feature sets and stimulus analysis, at the expense of synthetic processing of odor objects could just as easily impair discrimination and memory as impaired pattern separation (Mottron et al., 2006; Soulières et al., 2009; Figure 3).

As in the DG, environmental chronic stress impairs neurogenesis and reduces the population of newborn neurons in the olfactory bulb granule cell layer (Hitoshi et al., 2007). These findings suggest that chronic stress may also impair olfactory bulb pattern separation and odor acuity for highly similar odors. Olfactory impairments are associated with a wide range of disorders including mild cognitive impairment, Alzheimer's disease, Parkinson's disease, and schizophrenia. Normal aging can also both reduce OB neurogenesis and impair fine odor discrimination (Enwere et al., 2004). Although the level of olfactory bulb neurogenesis in humans is still debated, it is unclear why olfactory dysfunction would be comorbid with disorders having

such diverse etiologies. Thus, investigation of olfactory pattern separation in these disorders is warranted.

Conclusion

Here, we propose a common role in pattern separation for adult neurogenesis in the olfactory bulb and hippocampus. Specifically, in both regions, new granule cells may modulate inhibition of principal cells either directly (OB) or via interneurons (DG) and this inhibition may contribute to pattern separation. We also propose that different levels of neurogenesis represent an adaptation to environmental changes in cognitive demands such as those that take place with changing seasons, exposure to enriched environment, or in response to stress and adversity. When exaggerated, these adaptive changes may lead to pathologies associated with dysregulated pattern separation. For example, the excessive generalization observed in anxiety disorders may stem from impaired pattern separation while the excessive attention to details seen in individuals with autism spectrum disorders may result from excessive pattern separation.

Major questions remain unanswered. For example, if adult neurogenesis is such an effective strategy for promoting pattern separation, why is it not more widespread in the brain? Is neurogenesis the privilege of neural circuits devoted to encoding but not storage? Are there costs (such as erosion of memories) that preclude its inclusion in other circuits, or is adult neurogenesis in the OB and DG simply an evolutionary holdover not available to other regions (Kaslin et al., 2008)? Is the potential for neurogenesis latent in other parts of the brain? Addressing these questions will undoubtedly continue to transform our ideas regarding the regenerative potential of the adult mammalian brain.

ACKNOWLEDGMENTS

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