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Review

Paradox of pattern separation and adult neurogenesis: A dual role for new neurons balancing memory resolution and robustness

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ABSTRACT

Hippocampal adult neurogenesis is thought to subserve pattern separation, the process by which similar patterns of neuronal inputs are transformed into distinct neuronal representations, permitting the discrimination of highly similar stimuli in hippocampus-dependent tasks. However, the mechanism by which immature adult-born dentate granule neurons cells (abDGCs) perform this function remains unknown. Two theories of abDGC function, one by which abDGCs modulate and sparsify activity in the dentate gyrus and one by which abDGCs act as autonomous coding units, are generally suggested to be mutually exclusive. This review suggests that these two mechanisms work in tandem to dynamically regulate memory resolution while avoiding memory interference and maintaining memory robustness.
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1. Introduction

The brain continuously simplifies and integrates sensory experiences in the context of prior memories to generate the perceptions through which we interact with the world. We perform this integration most vividly as we conjure previous memories and compare and contrast them to our current experience, as is the case with highly salient episodic memories. On the one hand, we are able to differentiate between similar experiences, such as today's lunch and yesterday's. On the other hand, as with Proust's episode of the madeleine, an incomplete stimulus such as a single bite of a familiar meal allows us to mentally jump to another time and place, unleashing a flood of memories reconstructed from only part of the original experience. In reality, however, the brain is perpetually engaged in a parallel competition between new, discrete memory formation and generalization across similar experiences. Adult neurogenesis, the process by which new neurons are added to the dentate gyrus (DG) of the hippocampus (HC) throughout the life of an individual, is critical to the encoding and retrieval of these memories, particularly when the experiences are highly similar. This review focuses on the contribution of adult neurogenesis to the process of learning and memory and its possible role in permitting the hippocampus to dynamically and continuously optimize memory resolution and robustness.

2. Pattern separation by the dentate gyrus

The balance between discrimination and generalization is thought to be subserved by two competing processes: (1) *pattern separation*, the process by which distinct, but often overlapping or highly similar patterns of neuronal inputs are transformed into distinct neuronal representations, thereby allowing for the accurate formation of a new memory without interference from other memory representations, and (2) *pattern completion*, the process by which a full memory representation is evoked from a partial set of inputs that are often a subset of a similar but distinct memory or experience (Figs. 1i and 2i–iii). These computations are performed not through individual neurons but through the concerted activity of networks of neurons. Growing evidence indicates that the functionally distinct circuitries of each subregion of the HC differentially and simultaneously employ different balances of these processes to contribute their own degree of discrimination to hippocampal memory formation and retrieval (Fig. 1ii).

First among these subregions, the DG has been proposed as a "gateway" to the HC. Receiving non-spatial contextual information from the lateral entorhinal cortex (LEC) and metric spatial information from the medial entorhinal cortex (MEC), the DG compresses and conjunctively encodes multimodal sensory and spatial representations about the environment that are then passed on to the rest of the HC for processing (Hunsaker, Mooy, Swift, & Kesner, 2007; McClelland, McNaughton, & O'Reilly, 1995). These representations from the EC are transformed into sparse representations in

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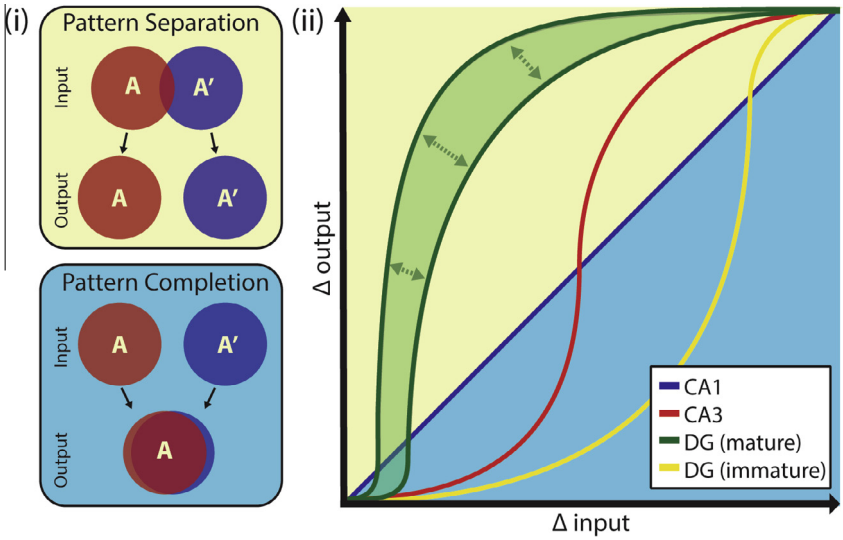

Fig. 1. Neurogenesis dynamically regulates pattern separation. (i) A schematic representation of pattern separation and completion. Pattern separation can be thought of as the process by which distinct, but often overlapping or highly similar patterns of neuronal inputs (A and A′) are transformed into more distinct neuronal representations, shown here as a decrease in overlap between A and A′. Pattern completion can be thought of as the process by which a full memory representation is reconstructed from a similar representation of partially overlapping inputs, represented here as A′ becoming more similar to A (Fig. 2ii), or from a subset of the inputs (Fig. 2iii). (ii) Nonlinear transformations for DG and CA3 by which each region initially pattern completes for nearby inputs but pattern separates for larger differences in inputs, each component contributing a different level of discrimination as Δ input is transformed into Δ output. The diagonal line represents equal differences in input and output, i.e., Δ input = Δ output. The region above the line represents conditions in which inputs are made more dissimilar (i.e., pattern separation), and the region below the line represents conditions in which inputs are made more similar (i.e., pattern completion). On the individual cell level, immature abDGCs integrate patterns across a wide range of inputs, resulting in pattern completion, with the ultimate result of dynamically modulating pattern separation in mature abDGCs on the network level. Adapted from Yassa & Stark, 2011.

the DG, as representations are expanded onto downstream dentate granule neurons (DGCs) that are 5–10 times more numerous than their upstream EC pyramidal neuron counterparts. This marked expansion of the neuronal population, extremely low inter-region connectivity (i.e., each DGC synapses on ~10 CA3 pyramidal neurons, two to three orders of magnitude less than the number of EC-DG or EC-CA3 synapses each EC pyramidal neuron makes; Amaral, Ishizuka, & Claiborne, 1990; Mulders, West, & Slomianka, 1997; Schmidt, Marrone, & Markus, 2012), and low intrinsic activity of the DGC population (Gothard, Hoffman, Battaglia, & McNaughton, 2001; Jung & McNaughton, 1993; O'Reilly & McClelland, 1994) are believed to allow for the formation of a sparse, distributed code. Traditional 'connectionist' or Hopfield-like network models suggest that the DG uses this sparse coding to increase the number of available representations by minimizing overlap between patterns of activity (Amit, Gutfreund, & Sompolinsky, 1987; Marr, 1971; McClelland et al., 1995; O'Reilly & McClelland, 1994; Treves & Rolls, 1994). Noting that where representations are not orthogonalized the system rapidly breaks down due to catastrophic interference (McClelland et al., 1995; McCloskey & Cohen, 1989), others have expanded these models to include an "error checking" function in CA3-DG feedback to avoid interference (Lisman, 1999; Rennó-Costa, Lisman, & Verschure, 2010).

While these connectionist models generally do not make strict distinctions between behavioral phases of encoding and recall, it has been suggested that, during memory formation, decorrelated patterns of activity undergo further enhancement before being transferred with relatively high fidelity from the DG to the CA3 through the mossy fibers to promote memory formation (Henze, Wittner, & Buzsáki, 2002; Urban, Henze, & Barrionuevo, 2001). In parallel, the relatively weaker but more active EC-CA3 perforant path connection provides direct input from the EC to promote memory recall (Lassalle, Bataille, & Halley, 2000; Lee & Kesner, 2004). It has therefore been proposed that, while the major functions of the HC are to encode and discriminate spatial and contextual events from one another, the sensitivity of the DG to small changes in input makes it particularly important when encoding highly similar stimuli and less important in promoting recall (Kesner, 2007; Lee & Kesner, 2004; though see a dissenting opinion in Nakashiba et al., 2012). It has been noted, however, that making a distinction between encoding and retrieval phases may prove difficult as learning and recall are fundamentally intertwined (Kesner, 2007; Rolls & Kesner, 2006).

These models can be conceptualized as a competition between the pattern separation of memory formation and pattern completion of memory recall (Fig. 1). A useful visualization for conceptualizing these attractor networks is a phase space diagram (See information box "Attractor Networks of Memory" and Fig. 2). Inputs, even if closely associated in phase space such as those on opposite sides of a "hill," can settle into different output states and be thought of as pattern separation (Fig. 2i). Inputs that settle into the same output state can be thought of as pattern completion (Fig. 2ii and iii). In the models above, the CA3 initially pattern completes, as recurrent activity leads similar inputs to recruit the same population of output neurons through attractor formation and thereby allows for the recall of memories (Fig. 1ii). However, the CA3 pattern separates if incoming inputs are similar but sufficiently distinct, represented here as a smooth phase space of long hills and troughs (Fig. 3i). On the other hand, the DG rapidly pattern separates as similar inputs are mapped onto distinct populations of output neurons, represented as a rougher, discrete phase space of sharp hills and valleys (Fig. 3ii), where only nearly identical inputs result in the same output (i.e., limited pattern completion). The DG contributes resolution for highly similar stimuli because it discriminates between fine details; however, the DG is

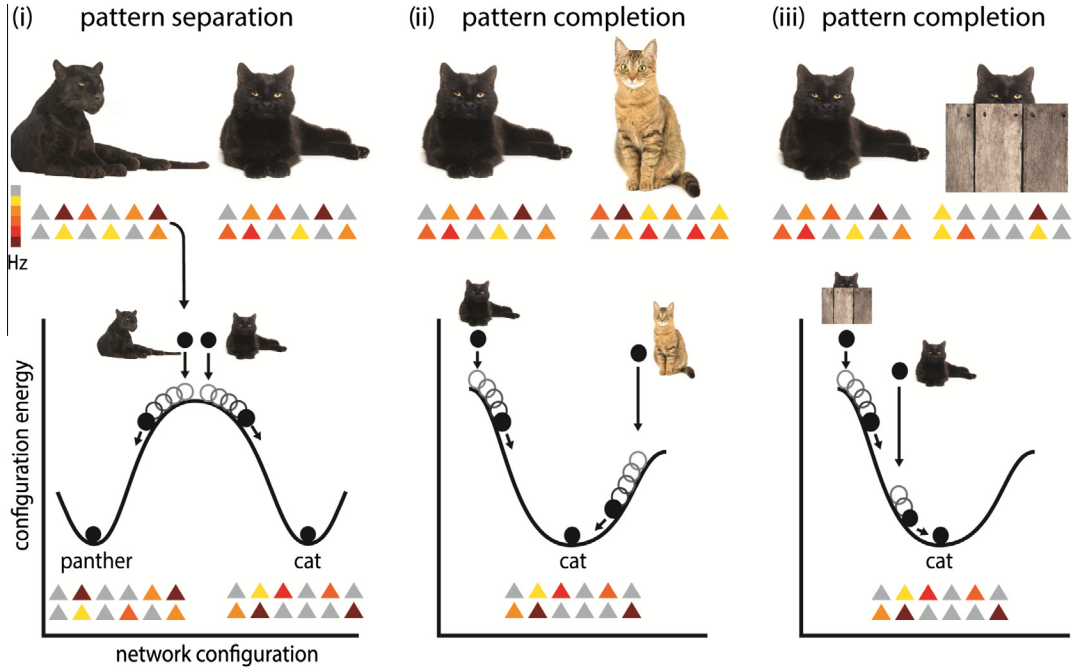

Fig. 2. Hippocampal pattern separation and pattern completion conceptualized in phase space. (i) Schematic of pattern separation where similar but distinct experiences, depicted by a black panther and a black cat, are encoded by similar patterns of neuronal network activity (network configuration). The network is optimized, presumably through synaptic plasticity during learning, such that neighboring input states separate and flow downhill to different low energy attractor states that are far apart in network configuration or "phase" space. These stable states are thought to code for percepts or other behaviorally relevant output of the network, such as "panther" or "cat". (ii) The energy landscape of phase space is complex and can also be shaped to encourage pattern completion, where distinct experiences are lumped together and generalized through convergence of their resulting network activity patterns. (iii) Alternatively, the same process can facilitate another form of pattern completion, where a full memory representation is evoked from a partial set of inputs.

likely unable to discriminate differences between small changes in input and large changes in input (Fig. 1ii). Both differences are already entirely orthogonalized (i.e., increasing the change in input does not increase the change in output), and the resulting overlap would not be greater than chance (Deng, Mayford, & Gage, 2013).

Behavioral support for the role of the DG as a pattern separator of highly similar stimuli first came in the form of lesion studies in which ablation or blockage of plasticity in the DG resulted in impaired discrimination of similar spatial and contextual information (Gilbert, Kesner, & Lee, 2001; Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; McHugh et al., 2007; Nakashiba et al., 2012; Saxe et al., 2007). The mechanism by which the DG actually performs this function, however, remains unclear. In vivo electrophysiological recordings suggest that, while small changes in environmental cues induce changes in the rate coding of DGCs, they do not result in the decorrelation of the population of active cells that the connectionist models above are predicated upon (Alme et al., 2010; Leutgeb, Leutgeb, Moser, & Moser, 2007). However, in agreement with the above computational theories, results from our lab and others employing immediate early gene (IEG) quantification as an alternate method of looking at entire populations of cells in the DG suggest that the DG rapidly decorrelates representations into distinct populations of DGCs with limited overlap to represent small changes in environmental inputs (Chawla et al., 2005; Deng et al., 2013). The relative strengths and weaknesses of these methods may make them inherently better suited to detect changes in rate or population coding. Electrophysiological recordings provide temporal resolution at the level of individual neuronal spikes, which can be directly correlated to a behavior as it is being performed. However, it is likely that all but the most active neurons in the dentate are recorded. Further, they lack the spatial resolution and cellular identification required to demonstrate population coding of the sparsely activated DG. In contrast, IEG methods provide spatial resolution and cellular identification. However, they lack temporal resolution, allowing only a single time point to be investigated, and minimal activity required which results in their induction remains unknown (Schoenenberger, Gerosa, & Oertner, 2009), preventing IEGs from being used to investigate rate encoding. IEGs also likely underreport total neuronal activity but may be less prone to neuronal noise. Despite these limitations, the literature still appears to be in conflict between rate and population encoding in the DG. It has been suggested that this conflict can be resolved by dividing the DG into two distinct populations (Alme et al., 2010; Deng et al., 2013; Neunuebel & Knierim, 2012; Piatti, Ewell, & Leutgeb, 2013). The first population is composed of the majority of DGCs, is sparsely activated, and is engaged in population coding; representations including these cells rapidly orthogonalize in response to small changes in environmental inputs and are missed by electrophysiological recordings. This population is likely mature DGCs. The second population of DGCs is more active, with signals frequent enough to be recorded in vivo, and does not rapidly orthogonalize. This second population of broadly tuned DGCs is proposed to represent hyperactive, immature adult-born dentate granule cells (abDGCs), and it may be missed by IEG studies (Huckleberry et al., 2015; Jessberger & Kempermann, 2003; Snyder, Glover, Sanzone, Kamhi, & Cameron, 2009; Snyder, Choe, et al., 2009). [An alternative explanation may be that, like CA1 and CA3, the DG uses alternate encoding methods to represent different types of information (Leutgeb, Leutgeb, Barnes, et al., 2005); however, these discrepancies may also be due to differences in behavioral protocols (Leutgeb, Leutgeb, Treves, et al., 2005; Wills et al., 2005). Such transitions between population and rate coding have not been directly tested in the DG.]

Attractor Networks of Memory

The attractor neural network (Poucet & Save, 2005; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005) is a theoretical framework useful for understanding ensemble neural activity and building intuition about the much theorized processes of pattern separation and pattern completion. Adapted from statistical physics, the state of the network is represented as a location in an abstract multidimensional space that describes all the possible configurations of the network (Fig 2). This *N*-dimensional configuration or ''phase" space is perhaps most easily conceptualized as being bound by *N* axes, each describing the firing rate for one of the *N* neurons within the network*. Each distinct combination of the *N* firing rates, or configuration, is represented by a unique point in phase space. Figs. 2 and 3 show schematics of this conceptualization in which each pattern of sensory stimuli or upstream neuronal activation results in a unique network state. However, while the initial state of the network is unique for a given set of inputs, the final state is not. Each of these configurations is assigned an energy describing the stability of the state of the network. Analogous to a ball rolling on a hilly landscape, the configuration of the network tends to flow toward local valleys that have lower energy. These stable network states exist in local energy minima and are thought to code for percepts or other behaviorally relevant representations of the network. Thus, depending on the roughness of the landscape, similar inputs eliciting network activity represented by nearby points in configuration space may (pattern completion, Fig. 2ii and iii) or may not (pattern separation, Fig. 2i) result in the same network representation. Presumably, the topology of the landscape, including the location of stable states and the roughness of their surroundings, is shaped through synaptic plasticity and other cellular and network processes in order to optimize computations relevant to the system (Fig. 3). As we describe below, it appears that the DG has been optimized to have a relatively rough landscape with a bias toward pattern separation, in which inputs that start off closely associated in configuration space are driven toward separate final states. In contrast, other areas of the HC, such as CA3, are smoother, facilitating pattern completion of similar upstream activity by driving similar inputs toward the same final state.

* In reality we do not know whether it is firing rate, spike timing, or other parameters that are truly relevant to the state of the network.

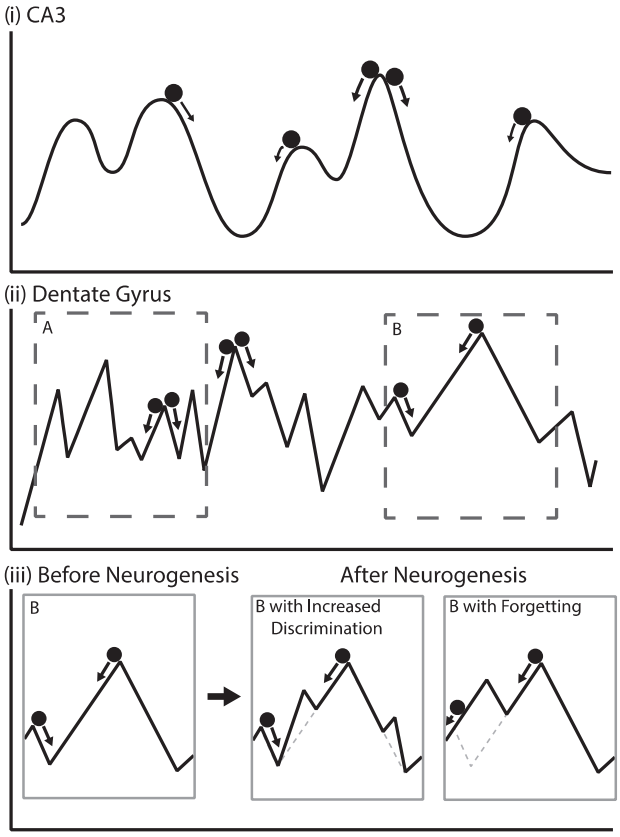

Fig. 3. Distinct roles for subfields within the hippocampal formation. Hippocampus-dependent memory formation and recall are constructed through a competition between *pattern completion*—driving similar inputs into the same attractor state—and *pattern separation*—driving similar inputs into distinct attractor states. (i) CA3 is represented as a smoother state space by which a large range of inputs leads to the same local minima, i.e., increased pattern completion. (ii) DG is represented as a rougher space with more discrete states. Small differences can lead to different local minima, i.e., increased pattern separation. Even within the DG, some of these spaces are smoother than others (A *vs.* B), permitting pattern completion at the cost of memory resolution (i.e., the fineness of discrete attractor states). (iii) Neurogenesis acts as an additional mechanism to increase resolution in these areas. A distributed code of overlapping mature DGCs sparsely encodes the input space into the output attractor space. Hyperexcitable immature DGCs, however, act as signal integrators to sample the state space and increase discrimination in low resolution (smooth) areas in an activity-dependent fashion by imposing "roughness" on the phase space, increasing the number of discrete states and adding local minima by acting as autonomous coding units and through disynaptic lateral inhibition. abDGCs may also increase rates of forgetting, conceptualized here as the replacement of one output state by another.

3. Neurogenesis is critical to pattern separation

Immature abDGCs undergo a critical period of increased excitability and enhanced plasticity (Espósito et al., 2005; Ge, Sailor, Ming, & Song, 2008; Ming & Song, 2011; Schmidt-Hieber, Jonas, & Bischofberger, 2004) as they begin to influence the activity of the local DG/hilar network and CA3. During this critical period, abDGCs have been shown to be behaviorally important for the encoding of new memories in the hippocampus (Dupret et al., 2008; Garthe, Behr, & Kempermann, 2009; Jessberger et al., 2009; Shors et al., 2001; Wojtowicz, Askew, & Winocur, 2008), with more recent studies demonstrating that, as animals undergo a variety of natural, genetic, and pharmacological manipulations of neurogenesis rates, their ability to discriminate spatial and contextual information is altered. This finding suggests that pattern separation within the DG is critically dependent upon adult neurogenesis.

Generally, when animals are subjected to decreases in neurogenesis, they are impaired in fine discrimination pattern separation tasks (Clelland et al., 2009; Clemenson et al., 2015; Nakashiba et al., 2012; Tronel et al., 2012), whereas increasing neurogenesis is sufficient to improve pattern separation (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; Sahay, Scobie, et al., 2011). However, contrary to this simplification, increasing neurogenesis may also result in a deficit in discrimination for easier tasks, apparently as the animal over-generalizes a response (Clemenson et al., 2015). Surprisingly, this deficit is rescued, with animals with increased neurogenesis outperforming controls if a more difficult task is implemented (Clemenson et al., 2015). These results suggest a more complex story in which not only the cognitive strategies of

animals is altered by experience-induced increases in neurogenesis but also HC connectivity, in which abDGCs have different inputs depending on the environment in which they matured (Bergami et al., 2015; Deshpande et al., 2013).

Techniques for altering neurogenesis rates do vary in magnitude and temporal selectivity, with some knockdown strategies such as focal x-irradiation producing near-complete and permanent loss of abDGCs (Mizumatsu et al., 2003; Monje, Mizumatsu, Fike, & Palmer, 2002) and others such as inducible transgenic systems that promote apoptosis sparing some of the newborn population (Deng, Saxe, Gallina, & Gage, 2009; Tronel et al., 2012) and allowing progenitor cell proliferation to rebound after the end of treatment (Deng et al., 2009). Genetic strategies are gaining popularity, but care must be taken to restrict expression to the desired population to obtain comparable results [Saxe et al., 2007 for example, uses a GFAP promoter with the hope of ablating radial stem cells which give rise to abDGCs, however this method is likely to have broad effects throughout the brain given extensive expression of GFAP in glia]. Properly targeted, genetic methods may hold promise for avoiding off-target effects such as increased inflammation (Mizumatsu et al., 2003; Monje et al., 2002) or inhibited angiogenesis (Kurzen, Schmitt, Näher, & Möhler, 2003; Monje et al., 2002), which accompany both irradiation and pharmacological knockdown methods. A common thread of behavioral differences in the ability to discriminate between similar events runs throughout recent studies of adult neurogenesis despite these variations in knockdown efficiency and off-target effects.

Taking the above results into consideration, descriptive models for the role of adult neurogenesis in pattern separation generally fall within two, often described as mutually exclusive, frameworks (Aimone, Deng, & Gage, 2010; Becker, 2005; Deng, Aimone, & Gage, 2010; Piatti et al., 2013; Sahay, Wilson, & Hen, 2011; Wiskott, Rasch, & Kempermann, 2006). The first model proposes that immature abDGCs act as individual coding units. As a consequence of low input specificity, immature abDGCs act as pattern integrators, responding to broad input patterns and rate remapping in response to subtle changes in an animal's environment. In turn, through their mossy fiber connections, they directly influence encoding in the CA3 (Aimone et al., 2010). As new neurons mature, they join mature DGCs as sparse coders in the DG and thereby contribute to pattern separation by encoding new representations in a new, orthogonal population of neurons, autonomously maximizing information while minimizing interference (Aimone, Deng, & Gage, 2011; Becker, 2005; Wiskott et al., 2006). The second model proposes a modulatory role whereby new neurons maintain the sparse activity of mature DGCs within the DG. Immature neurons mediate this function through their relative sensitivity to weak inputs. By reactivating for similar environmental stimuli – even if weak – they recruit feedback inhibition targeted toward mature DGCs, presumably via direct or indirect connections to local hilar interneurons (Sahay, Wilson, et al., 2011). This sparsity ensures minimally overlapping memory representations. Increasingly, evidence suggests a paradoxical dual role for adult-born neurons in both processes.

4. New neurons are pattern integrators/broad responders

During maturation, abDGCs go through a critical period of hyperexcitability, enhanced synaptic plasticity, and insensitivity to GABAergic inhibition (Gu et al., 2012; Li, Aimone, Xu, Callaway, & Gage, 2012; Marin-Burgin, Mongiat, Pardi, & Schinder, 2012; Zhao, Deng, & Gage, 2008) while still forming functional connections to CA3 similar to their mature counterparts (Toni et al., 2008; Zhao et al., 2008). During this critical period, immature abDGCs act as pattern integrators as they are activated in response to weak afferent stimulation and continue spiking, whereas mature abDGCs rapidly attenuate their response (Marin-Burgin et al., 2012). Behaviorally, new neurons are more likely to activate to novel stimuli (Kee, Teixeira, Wang, & Frankland, 2007; see Stone et al., 2011 for a dissenting opinion) but, more importantly, abDGCs are proposed to undergo stimulus-specific reactivation for stimuli that the animal experiences while the abDGCs are maturing (Tashiro, Zhao, & Gage, 2007; Trouche, Bontempi, Roullet, & Rampon, 2009). Expanding findings from Deng et al. (2013) to include reactivation of new neurons to enriched environments, results from our lab suggest the same type of preferential reactivation of immature abDGCs and preferential inactivation of mature abDGCs to contexts similar to those in which they matured (Deng et al., unpublished). Mossy fiber synapses further act to filter information coming into the CA3 (Henze et al., 2002; Urban et al., 2001), suggesting that the message hyperactive DGCs convey downstream is likely overrepresented (Alme et al., 2010; Gu et al., 2012; Marin-Burgin et al., 2012). As hyperexcitability declines, abDGCs no longer act as pattern integrators but undergo an abrupt shift and become physiologically indistinguishable from their sparsely activating mature counterparts (Brunner et al., 2014), now contributing to network function by representing the new information states they matured in (Aimone et al., 2011; Becker, 2005; Wiskott et al., 2006). Such new or novel states can be conceptualized in the phase space framework by the addition of discrete valleys to the state space (Fig 3iii).

5. New neurons maintain sparsity

Paradoxically, despite the role of hyperactive immature DGCs as input integrators, manipulations of adult neurogenesis inversely correlate with activity in the DG. Reductions of neurogenesis result in hyperactivity of the DG (Ikrar et al., 2013), and increased neurogenesis results in a suppression of activity in the DG (Ikrar et al., 2013), surprisingly without a change in activity levels downstream in CA3. In vivo, findings further suggest that decreasing neurogenesis increases coordinated activity in the DG (Lacefield, Itskov, Reardon, Hen, & Gordon, 2012), manifested at the cellular level as the recruitment of a larger population of DGCs in response to an environmental stimulus. The selectivity of DGC populations is compromised, leading to greater overlap between populations responsive to distinct contexts and accompanied by an overall increase in firing rate (Rangel et al., 2014). Overall, ablation of adult neurogenesis appears to reduce the inhibitory inputs that heavily suppress activity under normal conditions in the DG (Singer et al., 2011). Taken together with the behavioral studies mentioned above, these results are consistent with the theoretical prediction suggesting that DG sparsity mediates an animal's capacity to discriminate environmental stimuli in pattern separation tasks: hyperactive immature DGCs paradoxically maintain this sparsity and push the DG toward a system of greater pattern separation.

The mechanism by which abDGCs mediate this sparsity remains unclear. However, the balance of excitation to inhibition is likely to play an important role in this process. Immature and mature DGCs functionally innervate GABAergic interneurons that heavily suppress DG activity through feedback inhibition (Acsády, Kamondi, Sík, Freund, & Buzsáki, 1998; Li et al., 2013), whereas immature abDGCs themselves remain partially insensitive to GABA (Li et al., 2012; Zhao et al., 2008). In contrast to mature DGCs, recent work from slice physiology experiments has suggested that immature abDGCs may be limited in their ability to recruit feedback inhibition onto neighboring DGCs (Temprana et al., 2015). The implications of this work in vivo have yet to be clarified. Temprana and colleagues also showed reduced inhibitory drive to immature abDGCs via feedback inhibition from mature DGCs. Determining

whether this reduced feedback inhibition from mature DGCs and hyperexcitability of immature abDGCs counterbalances the immature abDGC's apparently reduced ability to recruit feedback inhibition onto the mature DGC network in vivo will require future experiments. Another recent study has suggested that immature abDGCs transiently form strong connections with inhibitory interneurons in CA3 (Restivo, Niibori, Mercaldo, Josselyn, & Frankland, 2015). Immediate early gene activation in 4-week-old abDGCs was also correlated with that of CA3 interneurons, suggesting that these two populations are coupled in vivo. This study relies heavily on morphological analyses, and physiological validation will be required to resolve this disconnect between slice and in vivo paradigms. The parallel maturation of abDGC-controlled inhibition and abDGC hyperactivity may, therefore, be all the more critical to ensure a balance between excitation and inhibition balance to ensure proper circuit function (Aimone, Wiles, & Gage, 2009; Clemenson et al., 2015; Weisz & Argibay, 2009; Weisz & Argibay, 2012). This balance is most apparent when attempting to interpret the results of Park, Burghardt, Dvorak, Hen, and Fenton (2015). X-ray ablation decreases evoked activity in the DG, suggesting a hyperactive role for abDGCs, but leads to a leftward shift in EPSP-spike coupling upon conflict training (a DG- and adult neurogenesis-dependent task), which the authors use to suggest an inhibitory role for abDGCs that is experience dependent (Park et al., 2015).

6. A dual role for new neurons: Balancing resolution and robustness

In the models above, inhibition mediates sparsity, and sparsity mediates discrimination by avoiding representational overlap. The DG, however, already has mechanisms to limit its activity. Heavy feedback inhibition from mature DGCs and mossy cells, as in much of the rest of the brain, does not have to be dependent on adult neurogenesis. Rather than merely playing a static role in pattern separation, adult neurogenesis may provide the DG with a mechanism to dynamically balance memory resolution and memory robustness by minimizing overlap between memory representations.

In this model, as the richness of an animal's experience increases and memory load becomes more complex, proliferation and survival of abDGCS might be expected to increase in an activity-dependent fashion (Park et al., 2015; Piatti et al., 2011; Stone et al., 2011). This increase in abDGCs results in an overall decrease in DG excitability (Ikrar et al., 2013) and ultimately results in increased sparsity via disynaptic inhibition of the DG network. This increased sparsity increases the number of nonoverlapping representations available to the network, in effect sharpening the state space to allow for increased discrimination and coding of new experiences. The ultimate result of these reallocations is to take smooth portions of the state space, in which it is difficult to discriminate nearby states, and impose roughness to increase memory resolution (Fig 3iii).

Increased sparsity, however, may come at a cost. As memory representations are distributed among fewer neurons, they may become more susceptible to loss through degradation and interference (Weisz & Argibay, 2012). Behaviorally, this process is manifested as forgetting. Recently it has been suggested that adult neurogenesis may mediate a unique form of forgetting (Akers et al., 2014). In this study, increasing neurogenesis after the formation of a memory was shown to inhibit recall of the learned experience, and the authors concluded that forgetting occurred. Adult neurogenesis may, however, permit increased memory resolution without sacrificing memory robustness by adding computational units to the circuit. However, behaviorally differentiating forgetting from increased discrimination may not be straightforward; that is, it is difficult to verify if an animal is *unable* to recall a stimulus or if it is now able to discriminate between two stimuli that the experimenter did not intend to make discriminatable. An animal may no longer see stimuli as equivalent because, as a product of increased pattern separation, it has become more sensitive to minor differences in the environment (Clemenson et al., 2015). Caution should therefore be used in interpreting results of any behavioral assay where forgetting and increased discrimination may lead to the same result. For example, Clemenson et al. used a fear conditioning discrimination paradigm in which the training (shock) context differed from each of two testing contexts. The wire grid floor used to deliver the shock was covered by a plastic insert in both testing contexts. An animal that has forgotten the original conditioning event will not freeze when exposed to the test contexts. However, neither will an animal that notices the floor has changed if it has specifically associated the foot shock with the floor. Similarly, performance during the probe trial of the Morris Water Maze is commonly reported as the percentage of time spent in the quadrant formerly occupied by the platform during training. An animal that spends little time in the target quadrant may have forgotten the original location, or may have been so certain of that location that it explored it once, found the platform to be missing, and continued searching the rest of the maze. To discount this interpretation, some groups report latency to the old platform location as well, but this is not universal. Alternatively, others have viewed these as changes in "cognitive flexibility" (Burghardt, Park, Hen, & Fenton, 2012).

According to the Mixed Coding Hypothesis (Aimone et al., 2011), immature abDGCs initially are low information encoders for broad content, but as they mature they become tightly tuned high information encoders, joining extant DGCs in a sparsely activated distributed code but now encoding novel stimuli, effectively adding new stable valleys to the phase space. The result is to allow the encoding of novel representations while avoiding overlap and interference with the surviving representational network. The task then becomes to differentiate the direct contribution of immature abDGCs, as "pattern integrators" heavily affecting learning and memory downstream, and mature abDGCs, as sparse encoders, from indirect effects on local network activity that then propagate downstream to CA3. These alternative models and behavioral outcomes listed above demonstrate that behavioral assessments of the role of adult neurogenesis are ambiguous when taken alone.

7. Looking forward

Recent work using opto- and chemogenetic manipulations have revolutionized our understanding of the substrates of memory "engrams" (Cowansage et al., 2014; Denny et al., 2014; Garner et al., 2012; Liu et al., 2012; Nabavi et al., 2014; Ramirez et al., 2013; Tonegawa, Liu, Ramirez, & Redondo, 2015). However, these experiments (like IEG experiments before them) have been limited in that they only label a single memory representation for manipulation. The means by which the patterns of activity are segregated and encoded remains unknown [though Nabavi et al. (2014) serves as the greatest evidence supporting a causal role for LTP in memory formation to date, and excitability at the time of encoding appears to influence the recruitment of a neuron into a memory representation; see Han et al., 2007; Han et al., 2009; Sano et al., 2014; Zhou et al., 2009]. The extension of calcium imaging to study memory in hippocampal behavioral tasks (Dombeck, Harvey, Tian, Looger, & Tank, 2010; Rajasethupathy et al., 2015; Ziv et al., 2013) is promising in that it may be the first technique to bridge the gaps between electrophysiological records and IEG experiments, in vivo, as an animal's memory is tested. It provides both the spatial and temporal resolution necessary to rigorously verify computational theories of pattern separation and completion while elucidating

questions about learning and memory as simple as, "What is the minimal unit of a memory?" However, basic questions such as these will not likely yield simple answers. Instead they will undoubtedly uncover complex dynamics as the brain attempts to balance anatomical, physiological, and environmental pressures to produce accurate predictions about, and generate appropriate actions to interact with, the world. A greater question for this system then becomes one of understanding the mechanisms and constraints under which these processes balance encoding and retrieval, discrimination and generalization, and remembering and forgetting. The role of adult neurogenesis, as a critical component of plasticity in the hippocampus when dealing with highly similar stimuli, is likely to yield interesting conclusions about the dynamic regulation of these forces.

Imaging alone, however, is likely insufficient and underscores a greater need for the development of complementary behavioral tasks. Ideal approaches will possess both the capacity to investigate how changes in sparsity contribute to memory resolution and robustness and the ability to target specific populations of abDGCs to further elucidate their direct and indirect contributions to network function. Further development in this area will, in turn, likely require a return to computational theories of pattern separation and completion to generate predictions about the circuit and network level activity that subserves these functions. "Behavior-free" passive imaging paradigms may also prove valuable, as minor network fluctuations may not be behaviorally observable. Future findings could lead to interesting questions such as "Does the animal or the dentate forget first?," as behavioral pattern separation and computational pattern separation, as performed through concerted network activity in the DG and HC, can be directly correlated (for differences between these two types of "pattern separation," see Santoro, 2013). This direction of study may prove all the more interesting as a tractable method to understand more generally how the brain tolerates variation in activity and how coordinated mass action gives rise to behavioral discrimination vis-à-vis pattern separation and completion. These findings will prove computationally relevant in many areas of the brain (Barnes, Hofacer, Zaman, Rennaker, & Wilson, 2008; Bartko, Winters, Cowell, Saksida, & Bussey, 2007a, 2007b; Burke, Wallace, Nematollahi, Uprety, & Barnes, 2010; Gilbert & Kesner, 2002; Gilbert & Kesner, 2003; Marr, 1983; Sahay, Wilson, et al., 2011; Wilson, 2009).

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Glossary

Adult neurogenesis: the process by which new neurons are continually generated from neural stem cells throughout adulthood. Known to occur in the subventricular zone (giving rise to olfactory bulb neurons) and in the subgranular zone (giving rise to dentate granule cells)

Attractor network: a recurrently connected network whose dynamics give rise to stable patterns (attractor states). Different initial states will settle into a final state that is a local energy minimum (for greater detail see Information Box "Attractor Networks of Memory")

Interference: the disruption or complete elimination of prior learning resulting from new learning. In networks, this results from the rapid adjustment of connections used for encoding the prior learning to accommodate the new learning

Pattern separation: the process by which distinct, but often overlapping or highly similar patterns of neuronal inputs are transformed into distinct neuronal representations

Pattern completion: the process by which a full memory representation is evoked from a partial set of inputs. A corollary of this idea is that similar neuronal inputs will result in the same neural representation

Resolution: the extent of information (or details) encoded by a network of neurons. Increased resolution increases the capability of the system to distinguish, find, or encode details

Robustness: the resistance of a memory representation to being lost, often through degradation and interference