**Adult hippocampal neurogenesis and memory interference: An update**

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**Introduction**

The hippocampus plays a crucial role in formation of episodic memories[1]. Formation of precise memories necessitates decreasing interference between representations of similar experiences so that each experience is encoded as a discrete representation and consolidated in hippocampal-prefrontal cortical networks. Pattern separation is a network computation that transforms similar inputs into dissimilar outputs and is thought to undergird the hippocampus' capacity to decrease interference between memory representations[2]. The dentate gyrus (DG)-CA3/CA2 circuitry is thought to play a crucial role in decreasing memory interference and serve as neural substrate for pattern separation[2-5]. Integration of a rich theory of dentate gyrus functions and development of viral and genetic tools to precisely target adult-born dentate granule cells (abDGCs) has significantly advanced our understanding of how abDGCs contribute to hippocampal-dependent memory functions. A consensus around a role for abDGCs in decreasing memory interference has emerged from these efforts. This perspective evaluates extant evidence for abDGCs in decreasing memory interference and the underlying circuit and network mechanisms. For more general and comprehensive critiques on contribution of abDGCs to memory, the reader is directed to several recent reviews [6-9].

**Dentate Gyrus and memory interference**

Foundational behavioral studies showed that chemical lesioning of the DG impaired a rodent's ability to distinguish between closely, but not widely, separated objects, suggesting a role for the DG in decreasing memory interference[10]. These findings were interpreted through the lens of how the DG functions as a pattern separator to decrease memory interference and support memory discrimination [11-13]. With development of cell-targeted genetic techniques, it was shown that synaptic inputs onto dentate granule cells is necessary for discrimination of similar contexts and remapping in CA3[14]. In vivo recordings in the

DG provided further evidence for DGCs and mossy cells in remapping, through changes in firing rate within a place field (local) or change in place-field (global remapping), a circuit mechanism that supports pattern separation[2,3,15-19]. Ensemble tagging studies also provided support for population-based coding mechanisms such as global remapping in memory interference tasks [20-24]. Showing that inputs are transformed into more dissimilar outputs, a hall mark of pattern separation, necessitates simultaneous recording of neural activity in EC and outputs of the EC, DG and CA3. Only one study has recorded from entorhinal cortex and downstream DG and CA3 in the same task, albeit in different animals, to demonstrate input-output transformation in EC-DG, consistent with a role for DG in pattern separation[4,18]. Under certain conditions, the DG may perform roles antithetical to pattern separation. Specifically, DGC activity was found to be invariant and stable in response to changing environments thereby functioning as a reference scaffold that potentially incorporates multiple experiences across time that have shared attributes [25,26]. This duality of DG functions may reflect different subpopulations of DGCs to support resolution of memory interference and memory updating or indexing functions [3,8]. These findings may also be interpreted through the lens of the re-registration hypothesis, an alternate mechanism by which DG encodes different environments. The re-registration hypothesis posits that contextual information is registered in population level activity underlying a context-invariant manifold that is coupled with a small number of context-sensitive spatially tuned cells [26,27].

Inspired by theory of DG function and rodent studies documenting a role for DG in decreasing memory interference, investigators devised incidental encoding tasks that necessitate resolution of memory interference to correctly distinguish between similar objects presented on a screen in the scanner [28-30]. These foundational human functional magnetic resonance imaging (fMRI) studies demonstrated that DG-CA3/CA2 activity was increased in individuals when they saw similar items rather than repeat presentations of previously viewed items. Notably, patient BL with a naturally occurring lesion of the DG demonstrated impaired performance in such a task [31]. Human fMRI has limited cellular resolution and cannot distinguish contributions of specific cell populations to the BOLD signal. However, an in vivo hippocampal recording study in monkeys revealed a sparse distributed code made up of activity of single DG/CA3 neurons as a substrate for memory discrimination [32].

**Adult-born DGCs and memory interference**

Using progressively more refined and specific (pharmacology, targeted x-irradiation, pharmacogenetic, genetic, optogenetic and chemogenetic) methodologies to manipulate the numbers and properties of

abDGCs, a substantial number of studies by many different laboratories converged upon a role for adult hippocampal neurogenesis in reducing memory interference in spatial learning tasks such as the Morris water maze, radial arm maze, touch screen task, spatial avoidance task, multi-object discrimination task and contextual fear discrimination learning task [8,22,33-47](For exceptions see [48] [49]). By increasing overlap in spatial features, goal-associated cues, contextual similarity, configural relationships between objects, or creating conflicts in learning rules in these tasks, an animal's ability to decrease memory interference is evaluated. The underlying premise is that successful behavioral discrimination necessitates neural circuit mechanisms that decrease overlap between neural representations. At the level of behavior, reducing the numbers of abDGCs or silencing abDGCs increased spatial memory interference [33,34,39-47,50], whereas increasing the numbers of abDGCs decreased spatial memory interference [8,22,36,37]. Contrasting a large body of work on abDGCs and spatial memory interference, much less is known about how abDGCs contribute to resolution of social memory interference. Consistent with the role of DG-CA3/CA2 circuit in encoding distinct representations of social experiences [51-56], abDGCs are necessary for formation of memories of social experiences [57,58]. We showed that genetic expansion of a single cohort of 4 weeks old, but not 8 weeks old abDGCs, decreased pro-active social memory interference to promote social memory consolidation [59].

The differentiation of immature abDGCs into mature abDGCs involves reorganization of input and output connectivity with diverse cell-types in EC, DG, CA3 and CA2 and changes in synaptic physiology and synaptic plasticity (Reviewed in [8,59-62], also see reviews in this compendium). Diligent and systematic characterization of maturing abDGCs has led to the proposal that unique synaptic properties and heightened synaptic plasticity of approximately 4-7 weeks old abDGCs enable these immature neurons to make distinct contributions to memory. Indeed, this prediction was borne out in behavioral studies designed to distinguish the contributions of immature versus mature abDGCs in decreasing memory interference [22,37-39,41,42,45,47,59,63]. In these studies, specific ages of abDGCs were ablated, genetically increased in number, chemogenetically or optogenetically manipulated to define stage-specific contributions of abDGCs to decreasing memory interference.

Analysis of ensemble properties and remapping in DG-CA3 following manipulations of abDGCs have generated key insights into how abDGCs decrease overlap in memory representations. Using ensemble tagging approaches such as cellular compartment analysis of temporal activity by fluorescent in situ hybridization (catFISH), genetic enhancement of adult hippocampal neurogenesis was shown to decrease overlap between context-associated DGC ensembles under conditions of high interference (highly similar contexts), but not same or distinct contexts (low interference)[22]. Chemical or genetic

suppression of adult hippocampal neurogenesis was shown to increase overlap of CA3 cellular ensembles when mice were exposed to similar, but not distinct, contexts[43]. Bidirectional regulation of levels of neurogenesis was also found to affect sparsity of activity in DG, a circuit property conducive to pattern separation[64]. Mice with increased neurogenesis showed a novelty- or mismatch-dependent suppression of activity in DG or increase in sparsity [22] whereas genetic ablation or silencing of abDGCs decreased sparseness under high conditions of memory interference [34,65]. Notably, several recent studies have examined the acute effects of manipulating abDGCs in vivo on circuit and network mechanisms governing memory interference. First, in vivo optogenetic stimulation or inhibition of immature, but not mature, abDGCs resulted in bidirectional changes in sparsity of hippocampal DG-CA3-CA1 network activity[47]. Second, chemogenetic silencing of immature, but not mature, abDGCs impaired rate remapping of spatial representations in DG of awake, head-fixed, behaving mice[41] and increased DG activity[63]. Thus, through their effects on sparsity and remapping, immature abDGCs, may decrease memory interference by increasing the likelihood that similar experiences are registered in non-overlapping ensembles. Increased sparsity facilitates encoding of contextual or mnemonic information in higher dimensional neural representations registered in uncorrelated activity patterns[5,66,67]. Taken together, these studies inform how immature abDGCs may contribute to pattern separation. However, a direct role for abDGCs in pattern separation necessitates simultaneous recordings from EC, DG and CA3 in mice in which abDGCs are manipulated in vivo.

**abDGC-dependent regulation of hippocampal network sparsity**

How does a small number of immature abDGCs exert a disproportionate effect on network properties such as sparsity important for reducing overlap (and interference) between principal cell activity patterns? In a 2011 perspective, we hypothesized that immature abDGCs modulate inhibition of mature dentate granule cells to influence sparsity and DG computations such as pattern separation[68]. Since that original conceptualization, numerous experimental studies, including those described in the prior section, have offered ex vivo and in vivo experimental validation for a role for immature abDGCs as modulators of hippocampal principal cell activity in DG [41,47,64,65,69,70] and downstream CA3-CA2-CA1 [47,59]. These findings underscore the need to instantiate the circuit mechanisms by which abDGCs perform this critical period-dependent modulatory role to influence activity of principal cells.

The connectivity architecture of inhibitory circuits in EC-DG-CA3-CA2 provides a scaffold for abDGCs to regulate hippocampal network sparsity through lateral inhibition of DGCs and feed-forward inhibition of principal cells in EC-DG, DG-CA3 and DG-CA2 [8,71]. The maturation of abDGCs is accompanied

by progressive recruitment of different classes of inhibitory neurons that sculpt dendritic (e.g.: somatostatin) and perisomatic inhibition (e.g.: parvalbumin) of principal cells [8,59-61,72,73]. In addition, abDGC recruitment of mossy cells enable long-range control of DGC excitability through the commissural-associational system[8,74-76]. Although there is evidence for direct connections between inhibitory interneurons, mossy cells and abDGCs, direct experimental evidence showing how abDGCs recruit mossy cells or engage distinct inhibitory circuits to reduce memory interference is still largely lacking. As a first step to bridge this knowledge gap, we recently showed that expansion of a single population of immature 4 weeks old, but not mature 8 weeks old, abDGCs resulted in increased feed-forward inhibition of CA2 and CA3 principal cells, reduced social memory interference and enhanced social memory consolidation [59] **(Figure 1)**. Expanding a single cohort of 4 weeks old abDGCs increased the power and duration of sharp-wave ripples, a neural substrate for memory consolidation[59,77,78]. Thus, we demonstrate how immature abDGCs preferentially recruit a circuit mechanism, parvalbumin-inhibitory neuron mediated feed-forward inhibition, to regulate principal cell activity[59]. Because feed-forward inhibition determines spiking fidelity of principal cells and expands the dynamic range of principal cell firing[79,80], such a circuit mechanism may enable immature abDGCs to increase hippocampal network sparsity and population dimensionality to facilitate discrimination[47] **(Figure 1)**.

Immature abDGCs compete with mature abDGCs for perforant path inputs [60,75,81] and successful synaptic integration of abDGCs may also increase sparsity in the DG [82]. Manipulations that promote synaptic integration of immature abDGCs also decrease memory interference but not memory forgetting [59]. Thus, synaptic integration of adult-born DGCs may decrease memory interference through sparsification of DG activity consistent with theory of input-expansion coding[2] **(Figure 1)**.

**Contribution of abDGCs to decreasing memory interference in humans?**

The perdurance of hippocampal neurogenesis throughout the lifespan of higher mammals continues to be debated [83] and conservative estimates suggest a precipitous decline in hippocampal neurogenesis in early life. However, direct and indirect evidence from non-human primates[84,85] and humans [86-91],respectively, suggest that abDGCs exhibit protracted maturation or neoteny such that abDGCs persist in an immature experience-modifiable state for a long period of time, from many months to years. Given what we have learned about the critical contributions of immature abDGCs to decreasing memory interference, neoteny of abDGCs in higher mammals may represent an evolutionary adaptation to compensate for the decline in neurogenesis. We recently proposed that neurogenesis in the DG increases the capacity and flexibility to generate indexes of experiences[8,92]. Neoteny of abDGCs may

facilitate the acquisition of features during maturation and thereby increase the diversity of information registered in properties and input specificity of individual DGCs. Modulation of principal cell activity by abDGCs may reduce interference between indexes in the DG and increase fidelity of memory encoding and retrieval. Formal evidence for how neurogenesis contributes to the library of indexes in the DG is still lacking. Modeling neoteny of abDGCs in rodent models as we have recently done will permit a critical evaluation of this thesis.

The role of DG in decreasing memory interference is conserved from mice to humans. Currently, we cannot non-invasively quantify or track abDGCs in vivo. How then does one examine the contribution of abDGCs to cognition? Critical to understanding how abDGCs contribute to memory will come from investigations of connectivity and physiology of non-human primate and human DG-CA3/CA2 circuitry [93,94]. Ongoing efforts suggest that the human DG-CA3 circuit exhibits conserved and divergent properties relative to rodents with important implications for pattern separation and pattern completion[93,94]. Identification of cell-specific enhancers that restrict cargo expression (reporters, actuators) to immature abDGCs will enable instantiation of circuit mechanisms. Ultimately, such efforts will determine the extent of conservation of this unique form of circuit and network plasticity in homo sapiens.

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**Figure 1. Circuit mechanisms by which immature abDGCs decrease memory interference**. For illustration, we focus on social memory interference. **a.** Social recognition necessitates distinction of new (orange) from previously encoded social representations (cyan) and reduction of interference by previously encoded social representations (purple). **b-c.** Immature adult-born dentate granule cells (abDGC) facilitate decorrelation of overlapping representations into distinct representations through increase in sparsity and high dimensionality coding in DG-CA3-CA2. Entorhinal cortex (EC) inputs are decorrelated in DG via feedforward inhibition and lateral inhibition. abDGCs compete with mature DGCs for perforant path inputs, exerting high levels of lateral inhibition onto other DGCs through local inhibitory microcircuits; this facilitates sparsification in the DG which establishes non-overlapping engrams for each social experience. abDGCs recruit feedforward inhibition to increase sparsity in downstream CA3 and CA2, support high dimensionality coding and facilitate transfer of engrams in non-overlapping populations of CA3 and CA2 principal cells. Following decorrelation of engrams of social experiences in DG-CA3/CA2, each representation is consolidated in independent cortical ensembles. Through these mechanisms, high levels of adult neurogenesis can reduce memory interference. **d-e.** Circuits with low levels of neurogenesis exhibit decreased synaptic competition, reduced feedforward inhibition in DG-CA3/CA2, decreased lateral inhibition and sparsity. This results in neurons with generalized encoding across social experiences, low dimensionality coding and increased interference. This increased interference results in overlap and linkage of representations of social experience during memory consolidation in the cortex.