Neurotherapeutics (2017) 14:630–645
DOI 10.1007/s13311-017-0539-6

REVIEW

Targeting Adult Neurogenesis to Optimize Hippocampal Circuits in Aging

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Published online: 23 May 2017

Abstract Millions of individuals suffer from age-related cognitive decline, defined by impaired memory precision. Increased understanding of hippocampal circuit mechanisms underlying memory formation suggests a role for computational processes such as pattern separation and pattern completion in memory precision. We describe evidence implicating the dentate gyrus-CA3 circuit in pattern separation and completion, and examine alterations in dentate gyrus-CA3 circuit structure and function with aging. We discuss the role of adult hippocampal neurogenesis in memory precision in adulthood and aging, as well as the circuit mechanisms underlying the integration and encoding functions of adult-born dentate granule cells. We posit that understanding these circuit mechanisms will permit generation of circuit-based endophenotypes that will edify new therapeutic strategies to optimize hippocampal encoding during aging.

Keywords Aging · Neurogenesis · Dentate gyrus · Hippocampus · Memory · Pattern separation

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Introduction

The world's population is aging, with ~20% of the US population expected to be older than 65 years in 2030 (up from 13% in 2010). Aging is associated with impairments across cognitive domains, including memory, attention, and executive function [1–4]. Cognitive decline affects a large portion of those > 65, where 12% of individuals self-reported increased memory loss in the preceding year [5] and nearly 60% of elderly study subjects showed cognitive decline over an 8-year study [6]. Clinically, memory impairments are diagnosed by performance on a number of tests, as well as self- and family reports [7, 8]. Aged individuals show select impairments in tasks requiring encoding new memories of events, facts, or contextual and spatial information, whereas short-term memory, autobiographical memory, and semantic and procedural knowledge remain relatively stable (reviewed in [1, 9]).

Aging also increases the incidence of pathological neurodegenerative diseases, including Alzheimer's disease and mild cognitive impairment (MCI), a clinical criteria used for early stage cognitive dysfunction preceding Alzheimer's disease. Similar memory impairments are seen in normal aging and MCI, although the deficits in MCI generally exceed those found in normally aging individuals [10]. Considerable evidence implicates dysfunction of the medial temporal lobe in age-associated memory impairments and MCI [1, 11, 12]. Notably, by examining aging across species that do not show neurodegenerative disease, age-related and disease-related impairments can be disentangled. Impaired memory has been described as a symptom of normal aging as it occurs across species [9]. Dissociating normal and pathological aging allows for the testing of empirical models to determine the neuroanatomical and functional basis of behavioral impairments, and the efficacy of age- or disease-specific treatments.

The identification of new therapeutics for age-associated memory impairments necessitates identification of underlying core neurobiological changes, both cellular and circuit-based. Hippocampal circuits support declarative or explicit memory function, and in humans this type of memory includes memories with a what–when–where component, including personal experiences and events that can be recalled and described, as well as spatial memory. In humans, our ability to assess age-related hippocampal changes is limited to behavioral measures, imaging analysis [including magnetic resonance imaging (MRI)/functional MRI (fMRI)], and postmortem histological assessment, whereas animal models with homologous hippocampal functions [13, 14], permit greater ability to interrogate the causal relationships between circuitry and behavior.

Here, we will present the case that disruption of dentate gyrus (DG)- and CA3-dependent operations such as pattern separation and completion, which are thought to underlie episodic memory formation, contribute to age-associated memory impairments. We describe evidence implicating the DG–CA3 circuit in pattern separation and completion and examine alterations in DG–CA3 circuit structure and function with aging. We discuss the role of adult hippocampal neurogenesis in memory precision in adulthood and aging, as well as the circuit mechanisms underlying the integration and functions of adult-born dentate granule cells (DGCs). We posit that understanding these circuit mechanisms will edify new circuit - based strategies to optimize hippocampal encoding in aged individuals. Furthermore, such efforts will permit generation of circuit-based endophenotypes that facilitate objective monitoring of symptom progression and treatment efficacy.

Memory Precision is Impaired With Aging

Episodic memory is particularly vulnerable to the deleterious effects of age. Older adults show deficits relative to young adults on tasks that require the formation of new episodic memories, including those with spatial and contextual components (reviewed in [1, 13, 15]). The literature on age-related memory impairments across species has been reviewed in detail elsewhere [13, 14], and data indicate that these memory deficits cannot be attributed to deficits in sensory, motor, or motivational deficits [16–18].

While many facets of memory are impaired with aging, growing evidence supports significant alterations in behaviors that require distinguishing among experiences that share similar elements, or conditions that require resolution of memory interference [14]. With aging, key changes in episodic memories are: 1) loss of contextual details (e.g., spatial or visual detail about stimulus location [19]); 2) susceptibility to interference (e.g., difficulty in remembering target stimuli when similar items or "lures" are used [20, 21]); and 3) a decreased response to new stimuli (e.g., impairments in identifying whether an item is new [22–24]; reviewed in [14, 25]). These deficits lead to specific memory errors, such as "false recognition" and a phenotype of "memory rigidity" [26]. It has been proposed that age-related deficits in memory precision may be due to alterations in neural mechanisms underlying memory formation and retrieval, such as pattern separation and completion (reviewed in [14, 25, 26]).

The DG–CA3 Circuit Supports Pattern Separation and Pattern Completion in Rodents and Humans

How does the hippocampus support creating new episodic memories that are distinct from similar, previously stored memories? Pattern separation is the computational process of making similar inputs less similar in output (i.e., orthogonalization) [27–29]. When inputs are very different, pattern separation is not required as the differences in input are sufficient to generate divergent outputs. However, when inputs are very similar (and thus likely to generate similar outputs) a computational process to generate distinct outputs is required to disambiguate these similar inputs. For memory encoding, this process is hypothesized to include encoding of new memories as nonoverlapping neuronal ensembles. Complementing the process of pattern separation is the process of pattern completion, defined as a network's ability to recall a complete representation when presented with incomplete or degraded input. While pattern separation and pattern completion are complementary processes, the DG performs pattern separation, and CA3 performs pattern separation or completion [30–33] (reviewed in [34, 35]). Recordings from DG and CA3 suggest that the DG automatically orthogonalizes inputs, and that it is the autoassociative network in CA3 that determines whether these inputs will be stored as a new memory pattern or if an old memory will be retrieved [35, 36]. Therefore, generating sufficiently orthogonalized information in DG and exporting this to CA3 is critical to avoid inappropriate pattern completion and incorrect memory retrieval.

Pioneering behavioral studies uncovered a role for the DG–CA3 circuit in resolution of memory interference (reviewed in [36]). Rats with selective lesions of the CA3 region were impaired in spatial discrimination of objects closely or widely spaced apart [37], whereas DG lesions produced impairments only at small separations, and CA1 lesions did not affect discrimination [38]. DG-specific *N*-methyl-D-aspartate receptor 1 deletion impaired discrimination of similar contexts [39], whereas CA3-specific deletion of NR1 revealed that CA3 is critical for memory retrieval when inputs are degraded [40]. These findings are consistent with the hypothesized role for the DG in pattern separation [27, 35] and with the postulated role for CA3 in pattern completion, which was based on its recurrent collaterals allowing the region to act as an autoassociative network (Fig. 1) [41–43].

Evidence for pattern separation requires demonstration of transformation of inputs into more divergent outputs at a

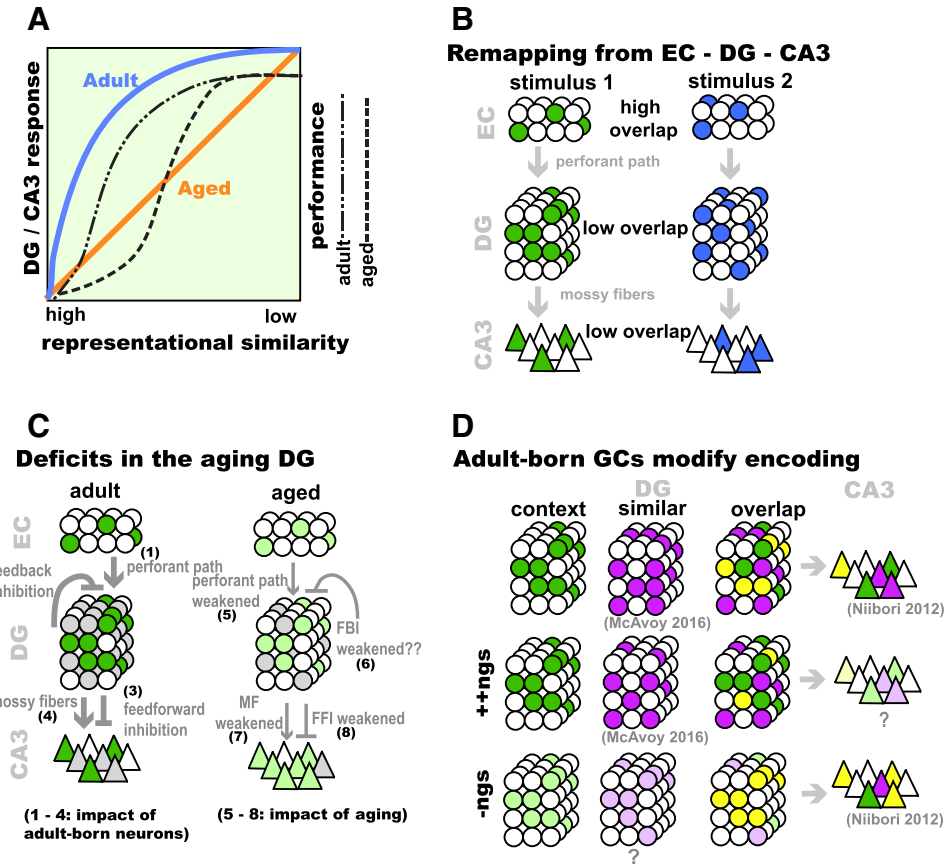

Fig. 1 Dentate gyrus (DG)–CA3 circuitry and pattern separation. (a) Schematic description of DG-CA3 blood oxygen level-dependent responses (left axis, blue and orange lines) and discrimination accuracy (right axis, dashed lines) in adults and aged individuals in a task in which image stimuli were presented and were varied on a continuum from repeat presentation, to similar items or lures, to novel foils (adapted from [14, 26], based on data presented in [23, 24, 72]). Aged individuals showed a failure to activate the DG–CA3 region when similar items or lures were presented. When explicitly tasked with identifying the images as novel or familiar, aged individuals performed more poorly when the images were most similar. (b) The DG performs pattern separation on incoming inputs from the entorhinal cortex (EC). The large number of DGCs relative to the EC ("input expansion") and the sparse activation of the DG are thought to facilitate the orthogonalization of similar inputs into distinct outputs. (c) The DG is modified by both incorporation of adult-born DGCs and by aging. 1) Adult-born DGCs may be more responsive to weak perforant path inputs. 2) Adult-born DGCs recruit feedback inhibition (FBI) onto the DG, and (3) feed-forward inhibition (FFI) onto CA3. 4) Adult-born DGCs exhibit increased plasticity at the DG–CA3 synapse. 5) In aged animals, perforant path inputs to DG are weaker, and feedback inhibition (6), and feedforward inhibition (8), may be decreased. 7) CA3 exhibites higher basal activity and hyperexcitability. (d) Adult-born DGCs promote population- based coding in DG and CA3. Enhancing adult hippocampal neurogenesis (ngs) decreases overlap between DG ensembles encoding similar contexts [118]. Decreasing adult hippocampal neurogenesis increases overlap between CA3 ensembles encoding similar contexts [146]

neural level. Pattern separation in the DG is supported by encoding of similar inputs by differences in firing rates of place cells (rate remapping) or recruitment of nonoverlapping ensembles of neurons [global remapping (Fig. 1); [33, 35, 44, 45]]. Knierim et al. [35] performed simultaneous recordings from entorhinal cortex (EC) and DG, and DG and CA3, as rats explored an environment in which local and distal environmental cues were gradually morphed. They showed that the DG remaps in response to small changes in context, under conditions where remapping in EC and CA3 remained unchanged [35, 44, 46]. A previous study had found that the DG also undergoes rate remapping for subtle changes in environment under conditions in which EC grid cell activity was unchanged [33]. Interestingly, the active cells with multiple place fields recorded in this study have been suggested to be hilar mossy cells and not DGCs [47–50]. Thus, DGCs and mossy cells may both contribute to pattern separation in the DG through different mechanisms.

Human studies have demonstrated that the DG–CA3 circuit is preferentially engaged under conditions of high memory interference [51–54]. Human imaging studies have taken advantage of the fact that repetition of the same stimuli suppresses blood oxygen level-dependent responses upon subsequent presentation (the repetition–suppression effect), and tested individuals with presentation of the same visual stimuli, novel stimuli (or "foils"), or similar stimuli ("lures") while the

subjects were engaged in an unrelated labeling task (e.g., categorizing objects as outdoors or indoors). Equivalent activation in response to targets and similar lures suggests hippocampal engagement for discrimination of the lures as novel stimuli, whereas the repetition–suppression effect indicates that the stimuli were perceived as repeat presentations. In contrast to CA1 and EC, similar levels of DG/CA3 activation in response to previously seen stimuli and lures was observed, indicating preferential engagement of DG/CA3 to discrimination of similar stimuli [51, 53]. Advances in imaging technology that overcome limitations in resolution will enable determination of input–output EC–DG transformations during these tasks.

Interestingly, a new study describes a patient, BL, with bilateral DG damage [55]. When given a visual recognition task similar to that described above, BL showed similar performance to controls when identifying novel and similar stimuli (lures), indicating intact recognition memory, but was 5 times more likely than controls to identify lures as previously seen stimuli. This indicates a deficit in resolution of interference, and was interpreted by the authors as a failure of pattern separation. However, in a second test that evaluates recognition memory performance with 10 drawings of rooms, 5 of which were familiar and 5 of which were novel, presented unmasked or masked to varying degrees, BL also showed a strong tendency to identify incomplete scenes as familiar, even when they were novel. The authors interpreted his poor performance identifying the unmasked images as indicative of a failure of pattern separation, as the image similarity presumably generated memory interference. Further, the authors note that patient BL's significantly worse performance on the degraded inputs (masked incomplete images) suggests a further bias toward pattern completion. These observations are consistent with the hypothesis that orthogonalized inputs from DG to CA3 are necessary to prevent CA3's attractor network from reactivating a previously stored memory pattern [35, 36].

Age-Related Changes in DG–CA3 Functions in Rodents

Aged rats demonstrate selective deficits in tasks requiring resolution of memory interference. Using a spatial memory test in which the animal had to distinguish a correct, learned reward arm from either a nonadjacent or adjacent nonreward "bait" arm, Gracian et al. [56] found that aged rats showed a particular impairment (relative to adult rats) when the nonreward "bait" arm was adjacent to the correct reward arm.

Deficits in behavioral memory precision may be due to failure to reactivate and remap neuronal ensembles. Experimental data in rodents substantiates the hypothesis that ensembles of cells encode information about spatial contexts. Reactivation of unique ensembles of DGCs previously activated (expressing the immediate early gene, *cfos*) by a particular context is sufficient to trigger context-specific behavior [57, 58]. In rats, CA3 and CA1 pyramidal neurons and DGCs fire during traversal of a limited portion of an environment (the "place field" of the cell; e.g. [59]). By reconstructing the firing patterns of many simultaneously recorded cells (the place cell map), the animal's location within the environment can be predicted (e.g. [60]). These maps are modified by experience-dependent changes in synaptic efficacy to allow for association of specific memory features (reviewed in [61]).

Aged rats fail to retrieve the same place cell "map" in CA1—retrieving the incorrect place field sequence for a second visit to an environment more often than do young rats with equivalent experience [62]. Further, aged rats failed to realign place fields to room cues, a feature that correlated with poor learning of a goal location [63]. Aged rats also showed reduced changes to CA3/CA1 place fields with alteration of the environment [64, 65], and showed reduced remapping in an entirely new context [65, 66]; CA3 cells, in particular, showed this "representational rigidity or inflexible remapping" and higher firing rates, in general [67]. To reconcile reports of incorrect map retrieval [62] and representational rigidity [64–67], Wilson et al. [68] recorded CA3/CA1 place cells during sequential exposures to a novel environment. They found that when aged rats were exposed to a new environment, CA1/CA3 place cell firing was initially unchanged, requiring greater environmental change to remap, followed by a period where the place cells became linked to the external cues (delayed relative to adult rats; see also [63]), and, finally, followed by a period where place cell ensembles showed incorrect map retrieval, analogous to that described by Barnes et al. [62] (reviewed in [9, 26]).

Using the catFISH technique (cellular compartment analysis of temporal activation using fluorescent *in situ* hybridization [69]) to compare ensemble overlap in the adult and aged DG upon re-exposure to the same context or upon exposure to a different context, Marrone et al. [70] found that there is less overlap in activation of DGCs upon re-exposure to the same context, indicating a failure to retrieve the appropriate map, reminiscent of CA3 place cell activity patterns in aged rats [62, 68, 70]. Importantly, this failure was limited to re-exposure to the same context, and was not seen with re-exposure to a different context in a different room. In a second task, rats explored an identical Y-maze in 2 different rooms sequentially, and were tasked with visiting a different novel arm in each room. Aged rats showed poorer performance relative to adults, which correlated with failure to reactivate a similar ensemble [70]. Thus, impaired ensemble reactivation in DG, as in CA3 (reviewed in [26]), in aged rats correlates with poor spatial memory precision.

In sum, data from aged rats suggest that CA3 fails to appropriately remap to novelty, and instead incorrectly retrieves previous memory patterns. Although technical difficulties have limited our ability to interrogate age-related changes in place field maps or in pattern separation in the DG,

considerable evidence implicates structural alterations in DG and CA3 that may underlie inefficiencies in ensemble reactivation and remapping in aging.

Age-Related Changes in DG–CA3 Functions in Humans

Aged individuals show specific deficits on tasks that engage the DG–CA3 circuit. In a test evaluating recognition memory performance with identification of complete or incomplete novel or familiar room drawings, aged individuals showed poor performance on discrimination of novel *versus* familiar stimuli, a phenotype construed by authors to reflect impaired pattern separation [71]. Further, aged individuals incorrectly identified degraded, novel images as familiar, suggesting a bias towards pattern completion, reminiscent of patient BL [55, 71]. In another visual recognition test in which individuals were presented with repeats of the same visual stimuli, novel "foils", or similar "lures", older adults showed poor discrimination accuracy when stimuli and lures were very similar, and exhibited comparable performance as adults only in discerning distinct stimuli [23, 24]. Interestingly, aged individuals exhibited increased blood oxygen level-dependent signal in DG/CA3 in response to both original or target stimuli, as well as lures [24]. Older adults also required more dissimilarity in stimuli and lures to decrease the DG/CA3 repetition-suppression effect [24, 25, 72]. Interestingly, individuals with MCI exhibited impaired discrimination of lures and elevated DG–CA3 activity during presentation of lures [73]. Newer approaches using ultra-high-resolution fMRI at 7 T and multivariate pattern analysis will permit assessment of DG and CA3 activation separately (rather than as DG–CA3) in aged individuals and individuals with MCI using these tasks [53].

Age-Related Changes in DG–CA3 Structure and Connectivity

The aged hippocampus does not show loss of principal cells in humans [74], rats [75, 76], monkeys [77], or mice [78] (reviewed in [9]), suggesting that age-associated memory impairment is more likely due to synapse loss and dysfunction. Consistent with this notion, the hippocampus is reduced in size in aged humans [79–81] (reviewed in [82]), and size correlates with deficits in explicit memory in aged individuals [83, 84]. Within the hippocampus, functional imaging studies suggest that the DG is the region most profoundly affected by aging in rats and macaques [85] (reviewed in [82]). In rodents, there is decreased EC to DG synapse number [86, 87] (reviewed in [88]) and decreased perforant path presynaptic fiber potential amplitudes [89]. Furthermore, long-term potentiation at the perforant path/DG synapse is more difficult to induce and shows reduced persistence in aged rats [90] (reviewed in [91, 92]). Concomitant with these EC-to-DG changes, there is a reduction in activity as measured by immediate early gene induction in DG following behavior in aged rats [70, 85, 93]. Diffusion-tensor imaging suggests a reduction in perforant path connectivity from EC to DG in aged humans [24, 72, 94–96]. Further, this reduction correlated with representational rigidity and poor behavioral discrimination in aged humans [72], further supporting the idea that changes in EC to DG connections drive aged-related impairments.

In contrast to decreased DG activation [70, 85, 93], CA3 shows hyperexcitability and elevated firing rates in rodents and nonhuman primates [67, 97–99]. Because mossy fibers of DGCs synapse onto inhibitory interneurons and CA3 pyramidal neurons [100, 101], decreased perforant path inputs onto DG (reviewed in [88, 92]) may reduce feed-forward inhibition from the DG to CA3. In addition, impaired plasticity at mossy fiber–interneuron synapses (reviewed in [102]) may underlie hyperactivity in CA3 [98]. Whole-cell recordings in CA3 indicate that the increased intrinsic excitability of aged pyramidal neurons is accompanied by a reduction in feed-forward inhibition onto CA3 [98]. Further, the number of inhibitory interneurons, particularly in the hilus, is reduced with age [103–105]. These findings suggest altered EC–DG connectivity and feed-forward inhibition from DG to CA3 may contribute to CA3 hyperactivation.

Adult Hippocampal Neurogenesis Decreases With Aging and Adult-Born DGCs Contribute to Pattern Separation

New DGCs are generated from neural stem cells in the subgranular zone of the DG throughout life (Fig. 2). Pioneering work by Altman and Das (1965) [106] first identified adult neurogenesis in the subgranular zone of the DG in rodents, and more recent studies have confirmed that the DG supports adult hippocampal neurogenesis in humans [107–111]. Adult hippocampal neurogenesis is exquisitely sensitive to circuit demands, and is tightly regulated by discrete, yet overlapping, mechanisms at multiple stages of neuronal maturation to ensure appropriate additions to the circuit (reviewed in [112–114]). In the subgranular zone of the adult DG, active neural stem cells give rise to transiently active neural progenitors, which differentiate into immature DGCs. Immature DGCs receive afferent connections in a stereotyped order [115–118], and the acquisition of these inputs is thought to govern their survival and integration into the hippocampus (Fig. 2) [118–122]. Adult-born DGCs between ~4 and 8 weeks of age exhibit heightened plasticity and are hypothesized to preferentially contribute to memory processing [118, 123–132].

Although adult neurogenesis declines slowly with age in humans [110, 111], it declines precipitously in mice, with 50% to 95% reduction between 6 weeks and 5 months (see, e.g. [118, 133, 134]; reviewed in [135, 136]). As this timeline is much faster than the acquisition of age-related memory impairments, it does not appear that declines in neurogenesis drives many aspects of cognitive decline [88, 137]. Nevertheless, if neurogenesis is important for encoding, then stimulation of

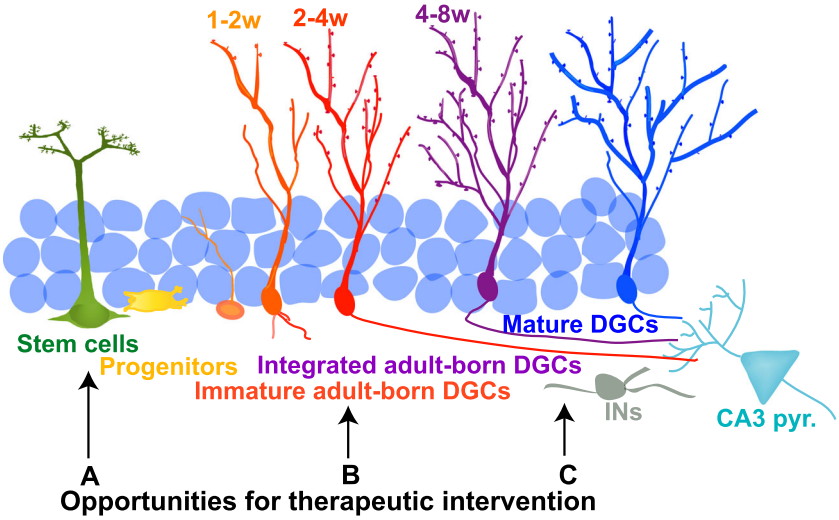

Fig. 2 Schematic of adult hippocampal neurogenesis and opportunities for intervention. Adult-born dentate granule cells (DGCs) arise from neural stem cells in the subgranule zone of the DG, with activated neural stem cells giving rise to transiently active progenitors, which differentiate into immature DGCs. Immature DGCs form afferent and efferent connections in a stereotyped order, and the acquisition of these inputs (initially γ-aminobutyric acid, and then glutamatergic inputs from the entorhinal cortex) governs their survival and integration into the hippocampus. Opportunities for therapeutic intervention to increase the adult-born DGC population or to mimic their effects on the circuit are highlighted: (a) removal of age-related molecular breaks on stem-cell activation and proliferation; (b) promoting integration of adult-born DGCs; (c) modulating DGC connectivity to increase feed-forward and feedback inhibition. *IN* Interneuron

neurogenesis may represent a therapeutic strategy to improve encoding in aging.

Ablation of adult-born DGCs impairs performance in behavioral tasks that require resolution of memory interference [138–146] (reviewed in [147]). Abrogation or reduction of adult hippocampal neurogenesis, or decreasing survival of adult-born DGCs, impaired discrimination of similar contexts [139, 141, 142, 148]. In a complementary series of experiments, deleting the proapoptotic gene *Bax* from adult-born DGCs, and increasing their survival, resulted in improved contextual discrimination [141]. Consistent with this finding, genetic silencing of the output of the majority of mature DGCs (4–5 weeks of age and older) resulted in improved contextual discrimination [139], suggesting that adult-born DGCs are sufficient for this discrimination. Interestingly, these mice were impaired in pre-exposure-dependent contextual fear conditioning and in using partial spatial cues to find a hidden platform in the water maze. These data suggest that mature DGCs may contribute preferentially to recall of memories based on partial cues, potentially through pattern completion [139].

Optogenetic silencing of adult-born DGCs during memory retrieval, or training in the contextual fear discrimination learning task, resulted in memory impairments [126, 149]. Interestingly, silencing adult-born DGCs during re-exposure to the trained, shock context had no effect on freezing, but silencing adult-born DGCs during exposure to the novel "safe" context prevented discrimination [149]. This suggests that adult-born DGCs may be required during encoding of a novel context.

Additional evidence for a role for adult-born DGCs in resolving memory interference comes from tasks using the radial arm maze and Morris water maze (MWM). Clelland et al. [138] showed that irradiation-dependent blockade of adult hippocampal neurogenesis produced deficits in both a radial arm maze task, in which mice had to chose a nonvisited arm from 1 of 2 options separated by varying degrees, and a touchscreen task in which choices varied by different spatial separations. In a complementary experiment, running, a proneurogenic intervention that also has other pleiotropic effects on circuitry, promoted performance on the touchscreen task [150]. Studies using the MWM have found that ablation of adult-born DGCs impairs spatial memory only when the target location of the hidden platform is reversed [143, 144]. In this reversal-learning portion, there is increased interference from the original location. Similarly, using a rotating platform in which a shock was given only in a particular quadrant, Burghardt et al. [145] found that ablation of adult-born DGCs impaired learning when the shock location was reversed. More recently, we engineered an inducible and reversible genetic system to modulate neuronal competition in the DG and enhance integration of 5 to 8-week-old adult-born DGCs [118]. In the MWM paradigm, increasing the population of 5 to 8-week-old adult-born DGCs had no effect on acquisition of initial platform location, but improved performance on the reversal portion of the task [118]. A direct, acute role for adult-born DGCs in resolution of memory interference comes from a study showing that optogenetic silencing of adult-born DGCs impaired a location discrimination task only

if the adult-born DGCs matured during the acquisition phase of the task [132]. Thus, in rodents, substantial evidence supports a role for adult-born DGCs in behaviors requiring resolution of interference, raising the question as to what are the neural mechanisms by which adult-born DGCs contribute to DG–CA3 circuit functions.

Circuit Mechanisms Underlying the Functions of Adult-Born DGCs in Memory Encoding

Adult-Born DGCs Exert Feedback Inhibition Onto the DG to Promote Sparseness

Adult-born DGCs may modify the activity of the entire DG by recruiting feedback inhibition that affects the mature DGC population (Fig. 1) [151–156]. Within the DG, activation of local interneurons is critical to limit the size of the neuronal ensemble [157]. Several converging lines of evidence suggest that adult-born DGCs recruit feedback inhibition. Lacefield et al. [158] found that the synchrony of gamma oscillations were increased in the DG of mice in which neurogenesis was ablated, suggesting that local inhibitory microcircuits are altered with ablation of adult-born DGCs. Using a genetic model to increase neurogenesis in combination with voltage-sensitive dye imaging in slices, we showed that increasing the adult-born DGC population decreased activity of the DG and increased threshold of activation of mature DGCs [152]. More recently, it was shown using channelrhodopsin stimulation of adult-born DGCs and whole-cell recordings that activation of the adult-born DGC population resulted in increased feedback inhibition onto mature DGCs [155, 159]. Interestingly, feedback inhibition was driven more strongly by 6-week-old than 4-week-old adult-born DGCs [159]. Further, middle-aged mice showed a dramatic decrease in feedback inhibition [155]. Using similar techniques, Restivo et al. [160] showed that activation of 6 to 8-week-old DGCs was correlated with activation of DG interneurons.

A recent study suggested that adult-born DGCs may modulate excitatory synaptic transmission onto mature DGCs (and, consequently, sparseness) through neuronal competition and redistribution of perforant path–DGC synapses. The authors found that genetic expansion of the adult-born DGC population by conditional deletion of the proapoptotic gene *Bax* in adult neural stem cells reduced excitatory postsynaptic currents (EPSCs) in mature DGCs. Conversely, genetically ablating adult-born DGCs increased EPSCs in mature DGCs [161].

Analyses of DG activity in awake behaving animals following manipulations of adult hippocampal neurogenesis has suggested a role for adult-born DGCs in modulating sparseness in a mismatch-dependent manner. Burghardt et al. [145] found that ablation of adult-born DGCs decreased sparseness only under conditions of high interference (reversal learning on a rotating shock task). *In vivo* recordings in the DG during this task revealed a reversal learning-induced suppression of DGC responses that was lost following ablation of adult hippocampal neurogenesis [162]. Recently, we showed using *cfos* catFISH that genetically enhancing adult hippocampal neurogenesis decreased overlap between cellular ensembles activated in response to exposure to 2 similar (high interference), but not same or distinct (low interference), contexts. Further, we found that mice with increased adult hippocampal neurogenesis exhibited a mismatch-dependent suppression of activity in the DG [118]. Together, these observations demonstrate a role for adult-born DGCs in promoting sparseness and population- based coding mechanisms, such as global remapping, underlying pattern separation in the DG (Fig. 1) [118].

Adult-Born DGCs May Modulate Feed-Forward Inhibition in DG–CA3 Circuit

Learning induces structural changes of mossy fiber synapses onto CA3 stratum lucidum interneurons and this form of structural plasticity correlates with memory precision [163, 164]. Maturation of adult-born DGCs is accompanied by reduction in DGC–interneuron connectivity, as 4 to 6-week-old adult-born DGCs exhibit greater connectivity with CA3 stratum lucidum interneurons [160] (N. Guo and A. Sahay, unpublished observations). Although adult-born DGCs recruit feed-forward inhibition onto CA3 *in vitro* [159], the functional significance of DGC–interneuron connectivity and its relationship with ensemble dynamics and population-based coding mechanisms remains poorly understood.

Clues to how adult-born DGC-dependent recruitment of feed-forward inhibition in DG–CA3 or DGC–CA3 stratum lucidum interneuron connectivity affects encoding come from studies examining the impact of manipulating adult hippocampal neurogenesis on ensemble activation during memory retrieval. A study using genetic ensemble labeling tools found that ablating adult hippocampal neurogenesis (by irradiation) or decreasing adult hippocampal neurogenesis (by a behavioral stressor) decreased ensemble reactivation overlap in CA3 when mice were re-exposed to the training context several days following training [165], reminiscent of a failure to retrieve context-appropriate ensembles [26, 62]. These findings are consistent with previous studies showing at a behavioral level that blocking [166–169] or enhancing adult hippocampal neurogenesis [170] decreases (or increases, respectively) the strength of long-term memory. Recent work from our laboratory [118] showing that expansion of the population of 5 to 8-week-old adult-born DGCs improved long-term contextual fear memory 4 weeks following training, lends further support to a role for adult-born DGCs in promoting long-term memory.

Analysis of population-based coding in CA3 using catFISH has shed light on how adult hippocampal neurogenesis may support pattern separation in CA3. Pharmacological or genetic reduction of adult hippocampal neurogenesis in mice resulted in an increase in overlap of cellular ensembles in CA3 when mice were exposed to similar, but not distinct, contexts. Interestingly, this increase in overlap was driven by increased activation of CA3, or decreased sparseness, when mice were exposed to the second context (Fig. 1d) [146].

Thus, adult-born DGCs may recruit feed-forward inhibition to dictate ensemble dynamics underlying long-term memory and global remapping in CA3. Further studies will delineate circuit mechanisms by which adult-born DGCs affect CA3 ensemble dynamics and whether increasing adult hippocampal neurogenesis during aging is sufficient to reverse failures of appropriate ensemble activation and remapping [26, 70].

Targeting Adult Neurogenesis to Improve DG–CA3 Functions in Aging

Promoting Integration of Adult-Born DGCs Into the Hippocampal Circuit

Previous studies have suggested that that stimulating neurogenesis throughout life improves memory in aging [171–177] (reviewed in [178]), although the correlation between levels of adult neurogenesis in aged animals and memory performance is tenuous [179, 180]. We sought to address the question of whether enhancing adult hippocampal neurogenesis in aged mice causally improves memory. To accomplish this, we developed a strategy to modulate neuronal competition and promote integration of adult-born DGCs without affecting olfactory bulb neurogenesis. Immature DGCs receive afferent connections in a stereotyped order [115–118], and the acquisition of these inputs is thought to govern their survival and integration into the hippocampus (Fig. 2) [118–122]. Activity of mature DGCs is thought to modulate survival of 1 to 2-week-old adult-born DGCs via hilar parvalbumin interneurons [181], whereas multiple lines of evidence suggest that ~2 to 4-week-old adult-born DGCs compete with mature DGCs to receive glutamatergic perforant path inputs to integrate into the circuit [121, 128] (reviewed in [113]).

We asked whether we could bias competition in favor of the adult-born DGCs by decreasing the spine density of mature DGCs [118]. Using an inducible and reversible genetic system, we overexpressed a negative regulator of dendritic spines, the transcription factor Klf9 [182], in mature DGCs. Klf9 overexpression decreased mature DGC spine density, and this resulted in profound increase in survival of competing adult-born DGCs. Virally mediated deletion of the cytoskeletal factor, Rac1, in mature DGCs produced a similar increase in the number of immature adult-born DGCs. These data support previous findings that ~2 to 4-week-old adult-born DGCs (the age at which they begin to receive glutamatergic inputs) are susceptible to competition-induced cell death [121]. Furthermore, our data are consistent with a study showing that genetic enhancement or ablation of adult-born DGCs decreases or increases EPSCs in mature DGCs, respectively [161].

We harnessed our genetic system to determine the impact of enhancing adult hippocampal neurogenesis during aging on encoding and memory precision [118]. We found that middle-aged and aged mice with enhanced adult hippocampal neurogenesis, unlike controls, were able to discriminate between 2 similar contexts when tested 1 day or 2 weeks after training. In addition, we assessed population-based coding in middle-aged mice. As with adult mice, expansion of the 5 to 8-week-old adult-born DGC population in middle-aged mice reduced overlap between DGC ensembles activated by similar contexts, suggesting that improved global remapping may underlie the improvements in behavioral discrimination (Fig. 1).

As stated earlier, it is unlikely that declines in adult hippocampal neurogenesis drive age-related memory decline. However, because adult hippocampal neurogenesis may promote "forgetting", or clearance of previously encoded memories [183] through neuronal competition, it is plausible that age-associated declines in adult hippocampal neurogenesis may drive cognitive inflexibility and impair resolution of memory interference.

Removing the Brakes on Neural Stem Cell Activation

Adult hippocampal neurogenesis declines with age (reviewed in [133]); however, the factors responsible for this decline are poorly understood. Humans show a less precipitous decline than rodents [111]. A number of reasons have been suggested for this decline: inability of the stem cell/progenitor populations to respond to proliferative signals (exhaustion of the stem cell niche [136], but see [184]), or reduced proliferation [185–187], lack of proneurogenic or plasticity factors [188, 189], or the presence of factors inhibiting neurogenesis—molecular 'brakes' [172, 174] (reviewed in [178]). Importantly, the aged stem cell population remains capable of increasing neurogenesis in response to exercise, neurotrophins, and systemic factors present in young blood (reviewed in [133, 178]). Further, recent work from our laboratory suggests that the aged neurogenic niche in the hippocampus is capable of responding to neurogenic stimuli and local circuit changes [118]. Overexpression of Klf9 in mature DGCs resulted in a decrease in mature DGC spines and an ~2-fold increase in survival of adult-born DGCs in adult, middle-aged, and aged mice. However, Klf9 overexpression, but not elimination of mature DGC spines alone, resulted in increased in neural stem cell activation. This increase in neural stem cell activation was significantly greater in middle-aged and aged mice than adult mice, suggesting that Klf9 overexpression in mature DGCs

may non-cell autonomously relieve a molecular "brake" that restrains proliferation in aged animals.

Multiple candidates for these age-related brakes have been suggested. The technique of heterochronic parabiosis entails surgically linking the circulatory systems of 2 animals of different ages, and has enabled identification of systemic factors present in aged blood that inhibit neurogenesis in young animals [172, 174]. In addition, the increases in microglial activation or corticosteroid levels in aged animals might negatively impact hippocampal neurogenesis. Microglia respond to inflammation [190], microglial levels correlate with the extent of neurogenesis in aged animals [191], and inhibition of microglia increased neurogenesis [192, 193], although the picture is still incomplete [194]. Further, corticosteroid levels ([195], but see [196]), and corticosteroid receptor expression on precursor cells [197] increase in older age and prevention of glucocorticoid-mediated effects maintains higher neurogenesis levels in aging rats [195, 198, 199].

Towards Healthy Cognitive Aging in the Future

Stimulation of adult hippocampal neurogenesis holds potential for optimizing DG–CA3 functions to maintain memory precision in aging, but major challenges remain (Fig. 3). Although our work suggests that increasing the population of adult-born DGCs in middle-aged and aged mice restores memory precision and improves global remapping, the question remains as to whether this strategy is applicable in humans. Modulating competition between mature DGCs and integrating DGCs provides selective, reversible control over adult-born DGC survival, but strategies to accomplish this in humans are currently lacking. However, activation of the perforant pathway has been shown to increase the survival of immature adult-born DGCs in mice [200], which may have functionally similar consequences on memory precision. As EC to DG connectivity is impaired with aging [96], such stimulation in aged individuals may have beneficial effects. While preliminary studies employing EC deep brain stimulation in humans resulted in improved memory performance [201], larger-scale studies have found memory impairments [202]. It is likely that further analysis and understanding of circuitry is required for successful implementation of EC stimulation protocols to improve memory in adulthood and aging.

Currently, several strategies identified in mice to promote neural stem cell activation or enhance neuronal survival might be applicable to humans. The Food and Drug Administration-

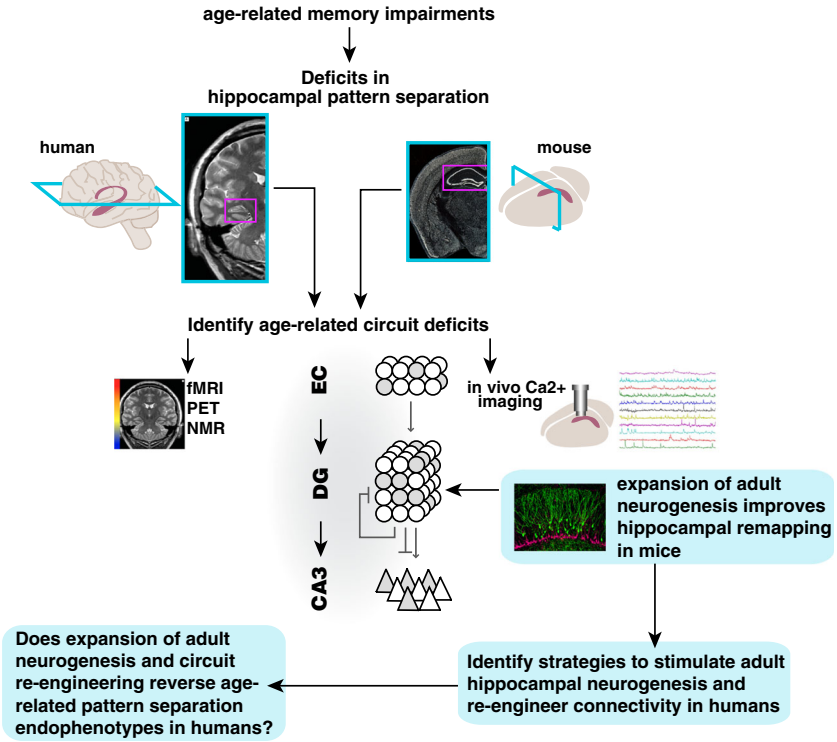

Fig. 3 Schema for how rodent studies edify novel therapeutic neurogenesis-based strategies to optimize dentate gyrus (DG)–CA3 circuit functions and improve memory in aged humans. Deficits in pattern separation/completion balance in DG–CA3 are observed/inferred in both rodents and humans, albeit at different levels of imaging resolution. Rodent studies permit elucidation of circuit-based mechanisms by which neurogenesis modulates DG–CA3 functions. Identification of circuit-based mechanisms facilitates development of strategies that target these mechanisms to promote DG–CA3 functions. Development of novel imaging approaches to visualize adult hippocampal neurogenesis or capture pattern separation at higher resolution will permit evaluation of efficacy of new therapeutic strategies. fMRI = functional magnetic resonance imaging; PET = positron emission tomography; NMR = nuclear magnetic resonance; EC = entorhinal cortex

approved diabetes drug metformin was shown to increase neurogenesis in mice [203, 204], as was the NMDA antagonist memantine [205], which has also shown efficacy in clinical trials for Alzheimer's disease (reviewed in [206]). Likewise, development of some small-molecule compounds that increase neurogenesis in mice may prove to have the same effect in humans [207]. Inhibition of inflammation or corticosteroids may mitigate some age-related decline in neurogenesis in humans as in rodents (reviewed in [208, 209]). In addition, exercise promotes neurogenesis in mice and may have similar effects in humans ([210]; reviewed in [211, 212]). Exercise has beneficial effects on cognition in aged humans [213, 214], although whether increased neurogenesis mediates the improvements is unknown (reviewed in [215]). The beneficial effects of exercise may be transmitted via exercise-induced, muscle-derived factors [216, 217] that act via promotion of neurogenesis [217].

Validation of these strategies to promote neurogenesis in humans will require the ability to visualize adult hippocampal neurogenesis in humans. This would allow efficient testing for correlations between behavioral task performance and levels of neurogenesis, with the goal of determining if increasing neurogenesis in humans improves memory performance in humans as it does in mice. Attempts have been made to image neural stem cells *in vivo* using MRI [218], but these remain subject to confirmation [219–221]. In addition, another study found measures of cerebral blood volume in mice correlated with increases in neurogenesis following exercise, and found similar increases in cerebral blood volume in exercising humans [222]. Another avenue is development of positron emission tomography ligands or tracers that would afford detection of neural stem cells or adult-born DGCs (Fig. 3) [223].

Increased understanding of how the connectivity of the DG–CA3 circuit causally relates to its function will inspire development of connectivity-based cognitive enhancers. As adult-born DGCs may contribute to DG–CA3 function through recruitment of inhibition, strategies to re-engineer connectivity between mature DGCs and stratum lucidum interneurons or directly promote inhibition onto CA3 neurons may bypass the need to stimulate neurogenesis ([147] and N. Guo and A. Sahay, unpublished observations). A note of caution: forced expression of molecules in developing circuits to rewire them may impair their functions. Overexpressing neuroligin-2 in adult-born DGCs increased their survival and synaptic contacts, but impaired memory performance [119]. Ultra-high-resolution fMRI at 7 T and multivariate pattern analysis will permit high-resolution assessment of how DG–CA3 circuit-based strategies described above impact pattern separation and completion in aged individuals (Fig. 3) [53].

Analysis of DG–CA3 connectivity, and age-related changes at the cellular level, would be facilitated by the development of empirical human models. The generation of human hippocampal neurons through direct reprogramming of fibroblasts, or directed differentiation of induced pluripotent stem cells, holds promise to delineate the neurobiological changes in aging at a cellular level [224, 225]. Although protocols have been pioneered to generate DGCs and inhibitory interneurons [226–228], we know much less about the ontogeny and process to generate CA3 pyramidal neurons. Ultimately, the generation of these different cell-types *de novo* or within organoids [229] will catalyze generation of human DG–CA3 circuits that permit high-resolution structure–function studies and facilitate identification of strategies to modulate connectivity at aged human DG–CA3 synapses. Further, these strategies will allow assessment of the contribution of human DGCs with different age-specific properties to excitation–inhibition balance. A detailed understanding of circuit mechanisms by which adult born DGCs contribute to encoding functions in adulthood and aging will ultimately edify new therapeutic strategies to combat age-related memory impairments.

Acknowledgments We thank members of the Sahay laboratory for their comments on the manuscript. A.S acknowledges grant support from US National Institutes of Health Biobehavioral Research Awards for Innovative New Scientists (BRAINS) 1-R01MH104175, NIH-NIA 1R01AG048908-01A1, 2017 NARSAD Independent Investigator Award, Ellison Medical Foundation New Scholar in Aging, Whitehall Foundation, Inscopix Decode award, Ellison Family Philanthropic support, and Harvard Neurodiscovery Center/MADRC Center Pilot Grant Award.

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