Adult neurogenesis and the dentate gyrus: Predicting function from form

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ARTICLE INFO

ABSTRACT

Hypotheses about the functional properties of the dentate gyrus and adult dentate neurogenesis have been shaped by early observations of the anatomy of this region, mostly in rodents. This has led to the development of a few core propositions that have guided research over the past several years, including the predicted role of this region in pattern separation and the local transformation of inputs from the entorhinal cortex. We now have the opportunity to review these predictions and update these anatomical observations based on recently developed techniques that reveal the complex structure, connectivity, and dynamic properties of distinct cell populations in the dentate gyrus at a higher resolution. Cumulative evidence suggests that the dentate gyrus and adult-born granule cells play a role in some forms of behavioral discriminations, but there are still many unanswered questions about how the dentate gyrus processes information to support the disambiguation of stimuli.

1. Introduction

The dentate gyrus (DG) of the hippocampus is among the most well-studied, and yet enigmatic, regions of the brain. Functionally, the hippocampus as a whole was revealed to be a critical region for memory, in large part due to a landmark series of studies of Henry Moliasion [1], an epilepsy patient who suffered profound amnesia and memory impairments following resection of large portions of his temporal lobe. Damage to the hippocampus has since been shown to preferentially impair declarative, episodic, and/or relational memories in humans and elicit deficits in the acquisition, consolidation, and time-limited recall of some forms of memory in other species. Despite the vast literature supporting the role of the hippocampus in the integration of information used to guide behavior, we are still working to understand how individual components of the hippocampus transform sensory information at various stages of the circuitry and how the unique properties of the DG support the overall function of this region.

The DG has a highly distinctive structure with a densely packed layer of granule cells and a neurogenic niche that supports continuous adult neurogenesis in most mammals examined to date [2]. These features have contributed to elaborated models of its function and formative hypotheses to drive behavioral neuroscience research related to hippocampal-dependent memory. Many of these features were

discovered through close studies of the anatomy or unexpected experimental results. But as technology improves and we are able to generate data at a higher resolution across larger brain regions, we can revisit the origin of some of the fundamental predictions about the computations performed by the dentate gyrus and how it integrates with other subregions to support memory encoding functions of the hippocampus.

Rather than deducing the function of the dentate gyrus and adult dentate neurogenesis through an extensive review of the literature that supports or refutes specific hypotheses, we will take a more historical approach in this review by chronicling some of the seminal observations that led to the development of these hypotheses. In doing so, we will highlight representative experiments that were based on these observations, as well as current controversies, with a focus on rodent studies. We will also discuss how technical advances have altered both the scale and precision of our observations, allowing us to make new predictions about the role of this phenomenon and subregion in hippocampal-dependent processes, and beyond.

2. Gross anatomy and physiology of the hippocampus and dentate gyrus

Considered to be an evolutionarily conserved region of archicortex,
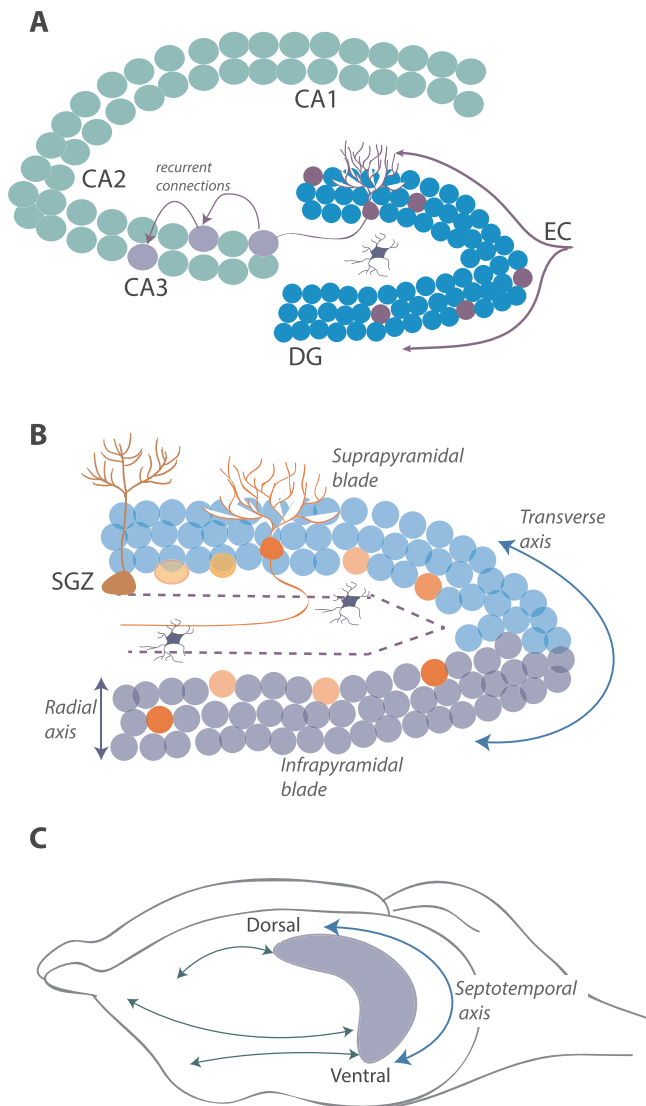
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Fig. 1. Emergent complexity and heterogeneity in the dentate gyrus. (A) Initial observations of dentate gyrus anatomy suggested a role for this region in mediating pattern separation of afferent input from the entorhinal cortex (EC) through expansion recoding, and a complementary role of pattern completion in CA3 due to recurrent connections. (B) The discovery of neurogenesis arising from neural stem cells in the subgranular zone (SGZ) revealed dynamic properties of the granule cell population with subsets of granule neurons co-existing at different maturational states. Functional differences have been identified in both the radial and transverse axes. (C) Retrograde and anterograde tracing revealed differences in long-range projections to and from the dentate gyrus, as well as within the dentate gyrus, along its septotemporal axis.

the hippocampus is a trilaminar structure with a distinct layer of excitatory projection neurons (Fig. 1A). Camera lucida drawings of Golgi-stained tissue by Ramon y Cajal and others illustrate the highly regular orientation of the pyramidal neurons, the principal neurons of the Cornu ammonis (CA) subregions, and the granule cells of the DG [3]. Lorente de No defined four distinct subregions, including CA1, CA2, CA3 and DG [4]. Within the hippocampus proper, the DG serves as the primary gateway, receiving most of the afferent information from the entorhinal cortex to the hippocampus. The classic trisynaptic circuit of the hippocampus describes the relay of signals from the entorhinal cortex to the DG then to CA3 and to CA1. Later studies have revealed additional complexity in this circuit including projections from both lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) directly to CA3 and CA1 and backprojections from CA3 to DG [5]. The

output from CA1 exits the hippocampus through the subiculum to impact widespread cortical and subcortical regions. Originally, it was thought that DG granule cells project only to area CA3 and not beyond, and that the boundary of CA2 could be delineated by the absence of DG input [6]. However, more recent studies revealed direct DG projections to CA2, including in mice and rats, but in a species-specific manner [7,8]. And in addition to local interneurons, there are also long-range projection interneurons that originate in the hippocampus [9] or target the hippocampus from distal regions [10].

2.1. Cellular morphology and synaptic structure

In the CA regions, pyramidal neurons comprise the sole excitatory and efferent cell population. Although the somatic morphology and dendritic structure can differ among these pyramidal neurons both within and across subregions [11,12], the general organization is that of basal dendrites extending from the base of the pyramidal soma, and a much longer primary apical dendrite extending from the apex of the soma with multiple branching tufts [13]. In contrast, the granule cells of the DG exhibit either a single, or multiple, apical dendrites that extend through the granule cell layer to branch extensively in the supragranular molecular layer [14–16], while basal dendrites are typically nonexistent in mature granule neurons in adult rodents under normal physiological conditions. A vast and heterogeneous network of interneurons innervates all hippocampal subregions, including the DG in which over twenty different subtypes have been identified based on morphology alone [17,18].

Morphological analyses of DG cells have also revealed distinct synaptic and topographical features with respect to the balance of GABAergic and glutamatergic signaling, which have functional implications for modulating excitation in the local network. Among the most prominent synaptic structures in the hippocampus are the efferent connections from granule cell axons, or mossy fibers, to the proximal dendrites of CA3 pyramidal neurons. Large presynaptic boutons on the mossy fibers align with extensive synaptic spine complexes on the postsynaptic cell, referred to as thorny excrescences. These dense multisynaptic structures have since been shown to exhibit morphological and electrophysiological bidirectional changes in response to global and local activity and may play a specialized role in gain control for homeostatic responses [19]. These potent synapses can also operate in a tunable detonator mode in which a single EPSP can trigger a spike in the CA3 pyramidal cell in certain contexts, for example, when primed by the occurrence of a preceding potentiation event [20].

In addition to these powerful glutamatergic connections with the principal excitatory neurons in CA3, mossy fibers also exhibit many small en passant synapses onto inhibitory interneurons within the hilus [21]. The mossy fiber of a single granule cell typically innervates up to 15 CA3 pyramidal cells but up to 40–50 interneurons in CA3 and up to 150 hilar interneurons, each of which can contact hundreds of excitatory targets [22]. Taken together, this suggests that a single granule cell can target individual CA3 pyramidal cells with high specificity and simultaneously exert a widespread effect on a network of interneurons that are distributed throughout the hilus and CA3 region, resulting in a net global effect of feedforward inhibition through strong lateral inhibition and targeted release at CA3 pyramidal cells. Further observations of the release probability and responses in both CA3 pyramidal cells and interneurons have shown that short bursts of firing from granule cells transiently increase the likelihood of firing in target pyramidal cells and induce longer-lasting potentiation in feedforward interneurons [23], while sustained firing in granule cells can induce short-term depression in interneurons, providing another strategy for dynamic control of targeted excitation [21].

Unique to the DG is a second excitatory cell population, the mossy cells, which were first identified from observations of the hilus in Golgi-stained tissue [18]. Mossy cells, so named for the appearance of thorny excrescences along their dendrites, make direct excitatory connections

to granule cells and interneurons ipsilaterally and contralaterally. Mossy cells receive input from granule cells at boutons, similar to the large synaptic structures at the granule cell to CA3 synapse. Although controversial for a period of time, the emerging consensus is that mossy cells are glutamatergic but exert a net inhibitory effect on nearby granule cells through extensive connections with the interneuron network, although the relative balance of excitation and inhibition may differ along the septotemporal axis [24]. Thus, in a similar way to the output of DG, mossy cell input to granule cells may gate information through a balance of targeted excitation and distributed inhibition.

2.2. Physiological properties across the subregions

Much of our understanding of the basic principles of hippocampal information processing in rodents is derived from electrophysiological studies that have identified hallmark properties that differ to varying degrees among the subregions. At the single cell level, the firing of many neurons in the hippocampus of rodents is spatially modulated and correlates with the location of the animal, independently of its behavior [25]. Pyramidal neurons in CA1 that fire action potentials primarily within a restricted location as rats explored their surroundings were first described in 1971 [26]. These place cells, and their corresponding place fields, were later identified in all hippocampal subregions with slightly different properties. There appear to be fewer place cells in CA3, but the place fields yield more spatial information [27]. For both CA1 and CA3, place cells typically fire in a single place field in a given environment and can exhibit remapping properties across different environments through changes in place field location (global remapping) or firing rate (rate remapping). In the DG, multi-field cells have been identified that were initially reported to be granule cells [28,29], but more recent evidence suggests that these may be mossy cells in the hilar region of the DG, which would be consistent with the more active basal firing properties of these cells observed in slice recordings [30,31]. In these later studies from rats and mice, most dentate cells that were classified or identified as granule neurons exhibit little to no firing in most environments. However, the small number of active granule cells typically fires within a single place field [30–32], suggesting that these cells are highly selective and support the encoding of environmental features in sparse populations. Imaging studies have also shown that identified granule cells have low rates of activity and are sparsely activated during behavior with variable specificity in terms of spatial tuning [33,34].

At the population level, periodic activity in different frequency bands of local field potential signals observed in all hippocampal subregions can reflect the general activity and behavioral state of the animal. Theta activity dominates when the animal is actively exploring, sniffing, and rearing, as well as during REM sleep, and is most pronounced in CA1 [35]. Gamma oscillations are more prominent in the CA3 and DG regions, and in the absence of theta [36]. There are additional features of coordinated firing that include sharp wave-ripple complexes in CA1 that occur when the animal is immobile, engaged in consummatory behaviors, or in slow-wave sleep [37] and dentate spikes in the DG that occur primarily during immobility and slow-wave sleep [38]. Many of these features have also been associated with various stages of memory acquisition, consolidation or expression.

3. Functional predictions based on anatomy

Different from nuclear structures in some parts of the brain, such as the amygdala or hypothalamus, the laminar structure and dominant trisynaptic circuitry of the hippocampus lends itself to predictions about its function based on the architectural organization of its cells alone. Interestingly, one of the most formative theories about the function of the DG is an extension of a model based on observations of another brain region, the cerebellar cortex. David Marr and James Albus each developed a theory of expansion recoding as a functional

property of the cerebellar cortex based largely on its anatomical organization [39,40]. Noting the relative abundance of cerebellar granule cells in comparison to afferent populations, they suggested that the cerebellar cortex may be optimized to encode discrete stimuli with minimally overlapping populations, supporting a pattern separation function to generate orthogonal representations of closely related inputs. Granule cells of the DG also outnumber their input cells, albeit by a lower ratio of approximately 5 to 1, or slightly higher at the poles of the septotemporal axis, leading to the idea that this is another region conducive to performing similar input-output transformations through sparse encoding [41]. In addition, CA3, the primary target of DG projections, has dense recurrent projections, suggesting that this subregion could support the complementary function of pattern completion. In contrast to pattern separation, which generates distinct neural codes to distinguish similar input patterns, pattern completion processes are thought to reinstate more complete activity patterns from degraded or partial input, effectively generating the same or similar outputs from different inputs. The storage capacity of CA3 for pattern completion relies on sufficiently distinct inputs, which would suggest that DG is anatomically positioned to provide this input to CA3 and that sparse activation of DG cells would support this function, which is a critical feature of the expansion recoding model.

3.1. Empirical testing of pattern separation

From a computational perspective, several recent studies have focused on input-output transformations at multiple levels in the DG to evaluate its potential role in pattern separation. In a simplified neuronal network model of granule cells, mossy cells and inhibitory basket cells, the degree of pattern separation was observed as a function of dendritic input, with the extent of dendritic branching in granule cells correlating with the sparseness in the activation of dentate granule cells [42]. In an effort to determine whether the transformation could occur at the single cell level, recent studies used slice recordings to show that the correlation of a set of output spike trains of an individual granule cell was lower than the corresponding set of input spike trains [43]. Interestingly, intrinsic properties of the granule cells were not a strong predictive factor of the capacity for pattern separation and instead the noise in spike output arising from short-term dynamics of synaptic transmission within the circuit was considered a likely contributor to the decorrelation. The decorrelation in granule cells was more robust than in interneurons in all conditions, and greater than in mossy cells over certain temporal integration windows. However, the output of CA3 pyramidal cells also showed significant decorrelation of inputs, especially at longer timescales. These results suggest that granule cells may not be the only cell type involved in either the computation or expression of discrete neural codes.

In vivo recordings of place cells in DG also support complementary roles of multiple cell types in the implementation of a pattern separation function. Recent studies have shown that dentate granule cells exhibit highly selective firing during spatial exploration of different environments, consistent with the classical view of pattern separation as expansion recoding with distinct subpopulations of granule cells active in each environment [30,31]. However, mounting evidence also supports a role for mossy cells in pattern separation, albeit through a potentially different mechanism. Mossy cells typically exhibit multiple place fields, which can change in both peak firing rate and spatial patterns across environments. In a cue mismatch task on a circular track, mossy cells showed stable firing patterns under standard conditions, but lacked a coherent population response when presented with large mismatches between local and distal cues [44]. In a treadmill task, both mossy cells and granule cells responded to small textural changes, with the mossy cell discrimination actually preceding that of the granule cells [45]. This suggests that mossy cells may play a role in mediating pattern separation processes in the DG, perhaps through modifying how the input to the granule cells is processed, as opposed to

merely receiving or amplifying distributed representations from the granule cells.

At the population level, many studies have relied on immediate early gene (IEG) activation as a readout of the degree of sparseness and/or overlap in the neural representation. Using activity-dependent and/or genetically-mediated tagging strategies, several studies have shown minimal overlap among dentate gyrus populations exposed to both similar and dissimilar contexts [46,47]. However, IEG activation and its detection at the protein level peaks around an hour after stimulation such that it reflects the past activation state of a given cell for a period of time. Thus, it can be difficult to disambiguate the particular stimuli that elicited the activation or the causal role of particular populations in establishing sparse representations.

3.2. Behavioral models

Many studies designed to test whether the dentate gyrus supports pattern separation have focused on behavioral assays that test the ability of animals to discriminate among stimuli with varying degrees of similarity. Typically, these experiments are conducted with a lesion of a brain region or manipulation of a cell population to demonstrate its importance for performing the discrimination. It is important to recognize that although this seems to be analogous to a computationally defined pattern separation function on an intuitive level, it does not necessarily imply expansion recoding to distribute neural representations over larger populations or that the properties of the same population are altered in distinctly graded ways during encoding. Animal behavior that reflects a discrimination among stimuli or contexts, which is disrupted or enhanced due to the manipulation of a particular population of cells, does not reveal whether in the intact condition there is a transformation of similar input to more dissimilar output at the neural level in the affected cells [48]. Nonetheless, many of these experiments have provided evidence that the DG may play a key role in the integration of information that supports behavioral discrimination. However, to determine whether computationally-defined pattern separation is a causal mechanism for this discrimination in the DG would require optical or electrophysiological monitoring in vivo to determine whether this population actively participates in the transformation, rather than being an essential relay in the circuit.

4. Adult-born neurons and unique plasticity in the dentate gyrus

One of the most distinctive features of the DG is its ability to support adult neurogenesis. Neurogenesis was not initially detectable from observing its anatomical structure alone through drawings or tracings of Golgi-stained sections of the brain, which failed to capture cells in the process of cell division. Indeed, Ramon y Cajal proclaimed the adult nervous system to be fixed and immutable. Evidence of neurogenesis in the adult brain was first established in 1962 through the use of intracranial injections of DNA thymidine analogs to label dividing cells [49]. In an unbiased survey of the brain of rats and adult cats, substantial labeling was observed in the DG following systemic injections of thymidine-H^3 [50], which declined with age in rats [51]. It has since been shown to be a robust phenomenon that occurs in most mammals, predominantly in the subgranular zone of the dentate gyrus and the subventricular zone of the lateral ventricles, which gives rise to a population of interneurons in the olfactory bulb [2]. Recently, the degree of adult dentate neurogenesis in humans has been a matter of debate [52] but in the rodent, adult dentate neurogenesis is robust, highly plastic, and dynamically regulated.

4.1. Morphological and synaptic development of newborn dentate neurons

Newborn neurons gradually acquire the stereotypical morphology of fully mature granule cells consisting of a primary dendrite originating from the soma that extends multiple branches. By 7 days, the dendritic arbor reaches the molecular layer, which is followed by robust growth for another 10 days, and further remodeling until the cells reach a developmental plateau at approximately 6–8 weeks old [53–55].

Synaptic development and integration of adult-born granule cells have been extensively studied and there are several reviews on the subject [56]. Briefly, it has been shown that GABAergic synapse formation precedes glutamatergic synaptic inputs in newborn neurons [53,57,58]. As is the case with early embryonic neuronal development, GABA initially depolarizes newborn cells due to the relative abundance of NKCC1 over KCC2 chloride transporters, which determine intracellular chloride concentrations and the polarity of GABAergic signaling. Therefore, the net effect of GABAergic innervation in cells up to 2–3 weeks is depolarizing, rather than hyperpolarizing [57]. This depolarizing GABAergic input arises from multiple interneuron types in the dentate gyrus including parvalbumin-expressing basket cells, somatostatin-expressing hilar perforant path-associated (HIPP) cells, molecular layer perforant pathway (MOPP) cells, and hilar interneuron with commissural-associational pathway-associated axon terminals (HICAP) cells [59–63]. Excitatory GABAergic input has been shown to support the survival of newborn neurons and promote dendritic and synaptic development and maturation [57,62,64,65].

As GABA transitions to becoming an inhibitory neurotransmitter beginning around 2 weeks of cellular age, glutamatergic synapses begin to form, arriving first from mossy cells within the DG, and then from entorhinal cortex afferents via the perforant path, preferentially from the lateral entorhinal cortex, and direct inputs from the medial septum via cholinergic neurons [59,63,66–68]. There also appear to be transient monosynaptic inputs from mature granule cells onto immature granule cells [63]. Structural and functional analyses have revealed that axonal growth of newborn neurons also occurs in distinct temporal phases. Adult-born granule cells make synaptic connections to CA3 pyramidal neurons, mossy cells and interneurons by 14 days and morphological development continues for approximately six additional weeks [55,69–72]. Recent data also suggest that newborn neurons directly and transiently innervate mature granule cells, but that these connections are eliminated after the adult-born cells mature [73].

4.2. Critical period of newborn neuron survival

In the adult rodent hippocampus, many newborn granule cells appear to die within 4 days due to microglia-mediated apoptosis [74] or between 1 and 4 weeks of age [75]. It is not clear why there seems to be a constitutive overproduction of adult-born granule cells that undergo regulated phases of cell death during the first 4 weeks, but this could be a mechanism to allow for rapid regulation of newborn neuron survival in response to changing environmental demands. Several studies have shown that experience can affect the survival of newly born and immature granule cells in the adult DG [76–78]. Beyond these early initial critical periods, it appears that adult-born granule cells do not undergo apoptosis in any significant numbers, and can be maintained across the lifespan in rodents [79–81]. In contrast, dentate granule cells born during early development do not appear to undergo an early critical period of survival shortly after birth [75], but are subject to cell death at much later stages in the adult brain, which may also be influenced by experience [82]. In humans, there is a renewed debate on the existence and magnitude of postnatal and adult dentate neurogenesis using classic markers of progenitor and immature cells in other species [83,84], but previous studies using BrdU labeling in human postmortem tissue [85] or carbon-14 to birthdate putative cell division events based on atmospheric carbon levels would suggest that there is significant adult dentate neurogenesis and that adult-born neurons in humans can be maintained for decades [86].

4.3. Critical period of synaptic plasticity

Perhaps the most pivotal discovery in the functional study of adult

hippocampal neurogenesis was the identification of a critical period of plasticity that occurs transiently during the maturation of newborn neurons. In slice recordings, it has been shown that newborn neurons between ~4 to 8 weeks of age have a lower induction threshold for long-term potentiation, a higher magnitude of responses, and are preferentially activated by afferent stimulation [87–90]. This plasticity is also uniquely dependent on NMDA receptors containing the NR2B subunit and does not require inhibition of GABAergic signaling [87,88,91]. In slice, afferent connections seem to functionally converge upon maturity by approximately 6 weeks, after which they appear to respond in a similar manner to glutamatergic and GABAergic inputs as perinatally born granule cells, although they continue to receive preferential input from the LEC [63,68,92,93].

This defined period of enhanced plasticity sets this population apart from most other cell types in the brain. Although many cells and populations may undergo changes in basal excitability, it is usually in direct response to stimuli or changes in the physiological state of the animal. For newborn granule cells, this period is intrinsically regulated to some degree and occurs as a process of maturation. Although some studies have shown manipulations that can accelerate maturation [94], it is unclear the extent to which the critical period itself is plastic in terms of being abbreviated or prolonged based on the animal's experience, similar to other critical periods that typically occur during early development. In slices, studies have been fairly consistent in defining the window of this critical period of plasticity with converging data suggesting that the age of 4 to ~6 weeks old is the peak time for the expression of this unique property in newborn granule cells. However, we still have little information on the duration and form of this plasticity for newborn granule neurons in vivo.

The observation of a critical period of plasticity in slices has led many to predict that newborn neurons at this age make a unique contribution to information processing in the hippocampus during this phase of hyperexcitability. Although the characterization of robust neurogenesis in the adult hippocampus [51] preceded some of the early theories of dentate gyrus function, investigation of this phenomenon languished for many years and was only later integrated with the parallel studies on pattern separation. The functional predictions about the role of the DG as a whole and adult-born granule cells have often overlapped, as in various permutations of the pattern separation hypothesis. Behavioral experiments with ablation or increases in neurogenesis have generally supported a role of this population in discriminating contexts and cognitive flexibility [95–99]. And computational models have shown how the activity and/or synaptic competition from adult-born neurons can enhance the detection of small differences in inputs [100,101]. In addition, there has been a debate about the relative importance of young vs fully mature granule cells in mediating the primary function of the DG [102]. What has been largely missing in the understanding of how adult-born neurons contribute to DG information processing is the experimental evidence showing how these excitable cells respond to environmental stimuli in vivo. Recently, an in vivo imaging study showed that mature granule cells exhibited sparse activity but robust remapping to contextual manipulations, whereas adult-born granule cells were more active at baseline and showed less spatial tuning, but also remapped to a similar degree [33]. This population level study supports both an increased responsiveness of newborn neurons, as well as the capacity to differentially respond to changes in environmental stimuli.

4.4. Circuit impact of adult-born neurons

In addition to needing higher resolution experimental approaches to determine how single granule cells manifest a critical period of plasticity in terms of firing rates, input transformation, and behaviorally correlated firing, another question that remains to be answered fully is how adult born granule cells modify activity within the local circuitry at the single cell or population level to support information processing at the network level. Recordings in slices have shown that the number of newborn neurons can modify excitatory transmission from the EC to mature granule cells and is inversely proportional to synaptic strength in the mature cells [103]. This supports the idea that newborn neurons compete for presynaptic targets and result in a redistribution of existing synapses instead of increasing the overall number of synapses within the local circuitry. Similarly, at a population level, increasing the levels of neurogenesis reduced the excitatory spread in mature granule cells in response to afferent stimulation and ablating neurogenesis had the opposite effect, presumably through modulating the excitatory drive to local interneurons [104]. Indeed, optogenetic stimulation of adult-born neurons was shown to excite GABAergic interneurons and evoke inhibition in mature granule cells, which could be enhanced through physiological stimulation of neurogenesis by exercise and diminishes with aging, when levels of neurogenesis are lower [105]. Cumulatively, these data support the idea that adult-born neurons could exert a net inhibitory effect on mature neurons to facilitate sparse encoding in this population.

4.5. Constitutive turnover in the population

One of the central unresolved questions in understanding the functional contribution of adult born granule cells relates to the constitutive emergence of immature cell populations. If all that was needed was a population of excitable cells to exert global inhibition via interneurons, a dedicated population of cells with enhanced plasticity and/or excitability would be sufficient. Instead, there is a constant turnover in the cellular identity of this population. What could be the advantage of having physically distinct populations of cells transitioning through critical periods and co-existing at different maturational states within the same network (Fig. 1B)? One idea is that the dynamic populations of newborn neurons contribute to encoding stimuli in a time-stamped manner, a critical component of episodic memory. Although some computational models have suggested that different cohorts of newborn neurons could provide information about the relative timing of different experiences, it is difficult to reconcile the timescale of the critical period, presumably lasting a few weeks, with a temporal framework for memory acquisition that would be informative in the long-term.

Rather than explicitly encoding temporal features at the population level, the more prevalent idea is that newborn neurons contribute to the encoding of all types of information processed in the DG. When thinking about newborn neurons as a neural substrate for discrete representations that support behavioral discriminations or pattern separation, there are at least two possibilities. One is that these more excitable cells are more responsive to a larger set of stimuli and encode stimulus-specific information that supports later recall of discrete representations. In this case, the newborn neurons themselves would instantiate the sparse representations that are relayed to CA3 [106]. This view suggests that there is a relationship between cell identity and sensory information that is retained for some period of time and may be reinstated upon re-exposure to the stimuli. Similar to studies that have shown activity-dependent tagging of hippocampal populations that support the encoding and/or recall of specific memories [107], one idea is that the newborn neurons could be the primary carriers of context-specific information. Specific cohorts of adult-born neurons may support the encoding of information and it has been shown that ablation of these neurons after training can disrupt subsequent recall and expression of some hippocampal-dependent memories [108].

Alternatively, immature neurons may provide some non-specific input to the circuit that supports the encoding of discrete representations in other populations. One such example of this role has been proposed to be the imposition of a global inhibition of mature granule cells that underlies their sparse activation [106,109]. Although electrophysiological evidence supports this role of newborn granule cells in conferring a net inhibitory tone in both DG and CA3 [105], which may be critical for pattern separation, it's not clear why different

populations of cells would be needed to perform this function. However, if there are transient properties of synaptic dynamics that occur exclusively in immature neurons such that both their connectivity and excitability contribute to their impact, this could help explain a unique time-dependent role of this population in information processing in the DG.

One possibility is that the newborn granule cells contribute to the synaptic noise that occurs in granule cells, mossy cells, and even CA3 cells, which could support the transformation of input to a decorrelated output at a single cell or network level [43]. Perhaps the general increase in excitability of newborn neurons, coupled with competitive and unstable synapse formation, leads to an increase in the stochasticity of firing in the postsynaptic cell, whether the targets are inhibitory interneurons or the excitatory cells of DG. In this way, the newborn neurons could contribute to pattern separation as a more general support mechanism to raise the level of neural noise and thereby increase the probability of generating decorrelated output in the information-carrying populations. The seemingly counterintuitive idea of increasing noise to increase the transmission of information has a long history in neuroscience and the role of noise has been shown to be beneficial at many biological levels and under many conditions. The classical notion of stochastic resonance in statistical physics, which describes the enhancement of signal detection in nonlinear dynamical systems due to an optimal level of noise, has been expanded in the context of biological systems to account for a wide range of phenomena and occasionally referred to more broadly as stochastic facilitation [110]. If variability in the synaptic transmission of newborn neurons to postsynaptic targets supports pattern separation in other DG populations through the addition of neural noise in the network, then the development of robust synaptic connections, as would result from Hebbian plasticity, would actually work against this function. In this sense, as the newborn neurons naturally develop more stable synapses over time, they may mature out of this role as a facilitator of pattern separation and a new cohort with less stable connections may be needed fulfill this role. Indeed, recent computational models suggest that Hebbian plasticity in the DG more generally does not support a pattern separation function in this region [111]. Eliminating or inactivating newborn cells at specific maturational stages during recordings of input-output transformations in single DG cells could help to resolve whether the immature neurons provide a level of noise in the system that contributes to pattern separation [43].

Interestingly, this notion of adult neurogenesis as a source of synaptic noise is also compatible with some of the results implicating neurogenesis with forgetting in early postnatal life and weakening of existing memories in later life [112,113]. If the activity of immature cells in the network exceeds a certain threshold, then the competition for existing synapses and variable input to target cells could disrupt existing connections. This would also suggest a need for calibrating the overall levels of neurogenesis through homeostatic mechanisms to ensure that the net impact of activity in immature neurons stays within an appropriate range to promote the sparse encoding and maintenance of specific information.

5. The role of the DG in different stages of memory

Although behavioral studies of the role of the DG have long focused on the initial encoding of information, recent studies have begun to decipher the role of the DG and adult-born neurons in different stages of memory and revealed a role for the DG in retrieval and extinction of learned associations [114,115]. And distinct populations of granule neurons have been shown to mediate the acquisition and extinction of learned fear [116]. At the electrophysiological level, a striking feature of the DG is the increase in neuronal activity observed from electrophysiological recordings during "baseline" periods of rest or sleep [30,117]. A study explicitly examining specific stages of sleep reported higher firing rates of granule cells during non-REM sleep as opposed to

activity recorded during REM and awake states [31]. Both dentate spikes and sharp-wave ripple complexes in CA1 are prominent during this sleep state, suggesting that the DG may play an influential role in memory consolidation or offline processing of information in the absence of stimuli. Behavioral studies investigating the role of the DG in memory consolidation have shown that dentate spike-triggered stimulation of the ventral hippocampal commissure after training impairs hippocampal-dependent associative learning in a trace eyeblink conditioning task, had no effect on spatial reference memory, and actually improved behavioral discriminations interpreted as pattern separation [118,119]. Similarly, expression of a contextual memory was impaired following inactivation of a small population of DG neurons with higher excitability due to genetic overexpression of CREB immediately following training, during the presumed consolidation period [120]. Because dentate spikes result in a transient decrease in CA1 and CA3 activity, these results suggest that the DG may modulate post-training consolidation processes in downstream hippocampal subregions in a task-dependent manner. It is interesting that this type of stimulation could have different effects depending on the nature of the memory and suggests that the putative pattern separation function may be more tolerant of nonspecific input, whereas the temporal encoding required for trace eyeblink conditioning is vulnerable to offline activation of cells that may not have been active during encoding.

6. Emergent anatomical distinctions

In addition to the functional distinctions among the anatomically defined hippocampal subregions, at least three major axes of the hippocampus, namely the longitudinal (or septotemporal), transverse, and radial axes, have been shown to differ with respect to their functional properties in rodents, illustrating more heterogeneity than was initially appreciated. All subregions have been shown to exhibit functional differences along these axes when investigated explicitly.

Perhaps the best characterized axis in terms of functional heterogeneity is the longitudinal axis with the broad generalization being that cells in the dorsal, or septal, pole in rodents are more closely associated with encoding of spatial features, whereas the ventral, or temporal, pole mediates the integration of information related to affective states (Fig. 1C). With respect to the DG, differences have been reported in afferent input from EC and backprojections from CA3 [121], the overall number of granule cells, the magnitude of neurogenesis, and IEG expression in both granule cells and mossy cells [122,123]. Behavioral differences based on selective manipulation of the septal or temporal regions have revealed differences in reward value encoding [124], contextual fear conditioning, and anxiety [125].

Along the transverse axis, anatomical connections from MEC and LEC differ in the CA1 and CA3 subregions, as well as the extent of recurrent connections in CA3 and backprojections from CA3 to DG (Fig. 1B). Spatially modulated firing properties also differ within these subregions, as well as in CA2 [126–128], and differences in memory encoding and retrieval associated with proximal and distal populations of CA1 cells have also been reported [129]. Distinct to the DG is the fact that its dense granule cell layer wraps around the proximal region of CA3 to create transverse anatomical subregions with respect to their position relative to CA3, namely the suprapyramidal and infrapyramidal blades. Anatomical connections to the blades differ with the suprapyramidal granule cells receiving more input from LEC while MEC preferentially targets the infrapyramidal blade [130]. There is also a slightly higher density of spines on the dendrites of suprapyramidal (1.6 spines/μm) as compared to infrapyramidal (~1.3 spines/μm) granule cells in the rat hippocampus [131]. Expression of IEGs has been reported to differ between the areas in an experience-dependent manner, as has the overall level of neurogenesis [132–135]. Newborn neurons are also differentially activated in response to spatial learning and novel context exposure, with generally greater numbers of immature cells in the suprapyramidal blade expressing IEGs following multiple context

exposures [136]. Interestingly, there appear to be blade-specific differences in the impact of physiological states on neurogenesis with chronic stress having a larger impact on the survival of newborn neurons in the suprapyramidal blade [137].

Finally, anatomical and functional distinctions have been reported in the radial axis of most subregions in terms of differences in MEC and LEC connectivity and spatially modulated firing of deep vs superficial pyramidal neurons [12,121,138,139]. The dentate gyrus exhibits perhaps the most distinctive difference along the radial axis in which neural stem cells reside in the subgranular zone at the junction between the hilus and granule cell layer. Adult-born neurons typically migrate to the inner third of the granule cell layer and have been reported to receive preferential input from LEC, rather than MEC [63], but it is not clear if this is due to their position along the radial axis or other properties of these cells that could influence the composition of afferent inputs.

7. Increased resolution of observations in single cells and distributed networks

Technological advances that are pervasive throughout neuroscience will also impact our understanding of the function of the dentate gyrus and adult-born neurons. At the single cell level, new sequencing approaches, such as single-cell RNA sequencing, have generated insight into the heterogeneity among cell types within classically defined populations such as pyramidal neurons [140,141] and GABAergic interneurons [142]. Coupling behavioral stimulation with transcriptomic analysis revealed sustained changes in a sparse population of granule cells activated during contextual fear conditioning [143]. Optogenetic tools have also allowed for the tagging and identification of neurons in vivo, which is essential to uncover the dynamic properties of individual neurons of a known cell type in behaving animals [144]. And improvements upon traditional methodology, such as simultaneous patch-clamping of multiple cells in the DG, has illustrated the extent of lateral inhibition mediated by interneurons acting on granule cells [145].

At a network level, tissue clearing technology holds the promise of generating additional insight into the long-range connections to and from the DG and adult born neuron populations that have been described in other 3D reconstructions of the region [55]. Functionally, we have yet to understand the extent to which afferent connections from extrahippocampal regions, such as the supramammillary nucleus [146] and medial septum [147], could impact ongoing activity in the DG. Neuromodulatory influences in the DG include cholinergic influences on learned behavior [148], noradrenergic modulation of plasticity [149], and endogenous opioid regulation of intrinsic physiological properties [150], but there are likely many other state-dependent effects on specific populations that play a role in the integration and transformation of multi-modal information into neural codes that support learning.

8. Summary

There is a growing appreciation of the extent of heterogeneity within hippocampal subregions and classically defined cell populations that would impact our understanding of how the hippocampus mediates the integration of complex information to form long-lasting memories. Far beyond a simple feedforward trisynaptic circuit between the EC and cortical structures, the hippocampus is a hub of neuromodulatory signaling, extensive inhibitory networks, and diverse anatomical connections along each of its axes. And given the ongoing birth of new neurons, the dentate gyrus is one of the most highly plastic anatomical structures in the mature brain and seems poised to make a significant contribution to these functions.

There is certainly extensive evidence to support the role of the dentate gyrus, as well as adult-born neurons of a specific age, in the discrimination of spatial environments and contexts to guide behavior,

but much work remains to be done to uncover a specific role of adult dentate neurogenesis in the active process of input transformation to generate minimally overlapping neural representations of specific features or configurations of stimuli. But the increased resolution of our tools to manipulate and observe specific cell types in the DG in vivo can lead to new insight into how various DG populations may act in concert to subserve higher-order functions and contribute to the formation of cohesive memories.

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