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Research report

Disambiguating the similar: The dentate gyrus and pattern separation

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ABSTRACT

The human hippocampus supports the formation of episodic memory without confusing new memories with old ones. To accomplish this, the brain must disambiguate memories (i.e., accentuate the differences between experiences). There is convergent evidence linking pattern separation to the dentate gyrus. Damage to the dentate gyrus reduces an organism's ability to differentiate between similar objects. The dentate gyrus has tenfold more principle cells than its cortical input, allowing for a divergence in information flow. Dentate gyrus granule neurons also show a very different pattern of representing the environment than "classic" place cells in CA1 and CA3, or grid cells in the entorhinal cortex.

More recently immediate early genes have been used to "timestamp" activity of individual cells throughout the dentate gyrus. These data indicate that the dentate gyrus robustly differentiates similar situations. The degree of differentiation is non-linear, with even small changes in input inducing a near maximal response in the dentate. Furthermore this differentiation occurs throughout the dentate gyrus longitudinal (dorsal–ventral) axis. Conversely, the data point to a divergence in information processing between the dentate gyrus suprapyramidal and infrapyramidal blades possibly related to differences in organization within these regions.

The accumulated evidence from different approaches converges to support a role for the dentate gyrus in pattern separation. There are however inconsistencies that may require incorporation of neurogenesis and hippocampal microcircuits into the currents models. They also suggest different roles for the dentate gyrus suprapyramidal and infrapyramidal blades, and the responsiveness of CA3 to dentate input.

There is a plethora of evidence linking the hippocampus with the formation of episodic memory (e.g., [27,28,71,94,103]). The process of encoding a new event, however, is one that is more complex than it may initially seem. To encode something as "new" one must be able to perform the fundamental process of deciding whether the current sensory stimuli related to a single event should be treated as the same as or different from other events in recollection, many of which may be associated with the same or highly similar stimuli. For example, we all have in our lives events that repeat in a relatively regular fashion. In the case of academics, this may include attending a class. Each time you visit the class, you are surrounded by the same people, who may even sit in the same relative location, and talk about the same subject. Yet, it may in your best interest to differentiate the lecture that occurred this week from the last one or the one before that. In order to do this, the brain must be able to successfully engage in a process that has been dubbed *pattern separation*: the ability to separate or orthogonalize similar events, as well as *pattern completion/compression*: treating two events as the same despite variation. How the hippocampal formation could accomplish both pattern separation and completion has been the subject of a great deal of research [29,38,68,69,80,86,109]. Much of this research has converged upon a family of theories and models that collectively attribute pattern compression/completion to the entorhinal cortex (EC) and/or CA3, while the role of pattern separation is typically made the domain of the dentate gyrus (DG), the topic of this review.

1. Linking pattern separation with the DG

The notion of pattern separation, as well as the DG as a critical mediator of this process, can be traced back largely to the early hippocampal model of David Marr [65]. Within this model, Marr proposed that area CA3 was ideally suited as a locus for memory storage and retrieval because this region's recurrent connections gave rise to what Marr termed the "collateral effect": the ability to store patterns of activity and later retrieve these same patterns if

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all or (importantly) part of the original pattern re-occurred. This idea was so influential that virtually every subsequent model of hippocampal function in memory has included some version of this role for region CA3. Work with this type of network quickly determined that the efficiency with which a recurrent network can store and retrieve patterns critically depends upon orthogonal input. As the correlation between patterns to be stored and selectively retrieved increases, the accuracy of retrieval in this recurrent network is compromised (e.g., [9,48,49,108]; but see [55]).

These data suggested the need for an additional structure upstream of the recurrent network to de-correlate incoming patterns and maximize the capacity of the network. The ideal placement of the DG to satisfy this requirement created an impetus for experimental data to confirm or refute this hypothesis. Over the course of the last 20 years, the overwhelming majority of data have supported the notion of the DG as a critical mediator of pattern separation within the hippocampal formation. These include anatomical data on the number and connectivity of principle neurons in the DG, electrophysiological recordings showing activity patterns consistent with the pattern separation hypothesis, and the effects of hippocampal lesions on learning in situations that are thought to depend on the type of pattern separation the DG is hypothesized to perform. We will present a brief summary of these data, followed by an examination of recent evidence based on patterns of gene expression and their implications for pattern separation function for the DG. Finally, several pieces of data that have recently emerged that are inconsistent with the pattern separation hypothesis (at least in the classical sense) as well as areas in which there is the need for more data presented as a guide for future research.

1.1. Behavior

When considering a behavioral correlate of pattern separation, discriminating highly similar contexts from memory, lesion studies of the DG provide empirical support for the DG's theoretical role [36,37,39,86]. In a study by Gilbert et al. [36] rats were trained to displace an object covering the food baited well. After a short delay the rats were returned to the maze and rewarded for displacing the object. However, an identical object was placed at varying distances (15–105 cm) from the original object. Rats with DG lesions were impaired at displacing the object at the correct location when the distance between the objects was small. This was not the case when the objects were placed far apart, consistent with the need to de-correlate similar sensory input.

A different type of behavioral support for pattern separation in the DG comes from a mouse strain lacking the gene encoding the N-methyl-D-Aspartate (NMDA) receptor NR1 subunit localized to the DG [67], essentially silencing long-term plasticity at these sites. Mice were trained on several hippocampal-dependent learning paradigms including contextual fear conditioning. Fear conditioned mice were tested for context retention in the original chamber and novel chambers. Mice lacking NR1 subunit in the DG showed normal contextual retention; however, they could not distinguish between similar retention chambers [67]. Conversely, when CA3 NMDA receptors were knocked out, mice were affected by the removal of a subset of cues in a familiar environment [75]. These data strongly support the roles of plasticity in the DG and CA3 as critical to pattern separation and pattern completion, respectively.

Recent studies using high resolution functional magnetic imaging have also supported the role of the DG in pattern separation in humans. Due to spatial resolution limitations CA3 cannot be distinguished from DG activation, however comparisons can be made with EC and CA1 activity. Bakker et al. [10] had participants identify a picture as one originally seen, a slightly different version of a previously shown item (lure), and a novel item. Accurately differentiating the lure with the target object would provide evidence for pattern separation. When presented with the lure item, the bilateral DG exhibited differential activity than with repeated presentation of an item. Differential activity was not seen upstream (the entorhinal cortex) or downstream (CA1 and subiculum) of the DG. Similar results have been reported by others [56,119]. Taken together, these data indicating a role for the DG in distinguishing between similar inputs in both humans and rodents support the idea that the DG engages on a similar de-correlation function across species.

1.2. Anatomy

For the DG to play a critical role in pattern separation, several anatomical constraints must be met. Investigating whether the projections satisfy these requirements has been extensively investigated (e.g., [80,108]). An exhaustive summary of the anatomical features is beyond the scope of the present review (see [6,7,116]); however, some of the most salient of these features will be described. Afferent input from EC is serially processed in the hippocampus proper via the trisynaptic circuit (EC → DG → CA3 → CA1; Fig. 1a). Although there are other projections that bypass this tri-synaptic circuit (reviewed in [116]) and under certain conditions can support memory [16,84], the DG is the first terminal of this major circuit [6]. The DG is situated around the hilus and tip of CA3, thus divided into the suprapyramidal (below CA1, enclosed) and infrapyramidal (below CA3, exposed) blades.

1.2.1. Cell numbers

Given its highly convergent input from several cortical areas onto a limited number of cells it is thought that the EC supports redundancy compression (e.g., [29,38]). More importantly in the context of this review, the rat EC is composed of ~675,000 principle neurons [70,74], ~112,000 pyramidal cells located in layer II of the medial EC and lateral EC project to the DG [74], which is comprised of over 1,200,000 granule neurons [5,74,83,115]. The main target of the DG, hippocampal area CA3, has ~250,000 pyramidal cells [5,14,74]. Thus, based on cell population size, there is a divergence from the EC to the DG, followed by a convergence to CA3 (this is altered along the longitudinal axis, see below).

1.2.2. Connectivity

One granule cell targets ~15 CA3 pyramidal cells and each CA3 cell receives convergent input from ~72 granule cells [116] (Fig. 1b). Given the large number of granule cells and connectivity to CA3, the probability that an individual CA3 cell will receive inputs from two active granule cells is very low [5,68,69]. Consequently, input from the neocortex gets distributed among granule cells and can converge back onto CA3 forming a new representation.

1.2.3. The longitudinal axis

The above findings pertain to the dorsal (septal) regions of the hippocampal formation. Though the pyramidal cell density is conserved along the longitudinal (dorsal–ventral) axis in the EC [35], the situation changes along the longitudinal axis of the hippocampus. Moving from the dorsal to ventral (Fig. 1c/d) poles, the density of granule cells decreases and the density of CA3 pyramidal cells increases. Therefore, the ratio of granule cells to CA3 pyramidal cells is 12:1 in the dorsal hippocampus and 2:3 in the ventral hippocampus [34]. Given that the contact probability of mossy fibers on the CA3 pyramidal cells is consistent along the dorsoventral axis, contact probability is much lower in dorsal hippocampus [6]. Moreover, backprojections from CA3 to the DG also change with location on the longitudinal axis. Ventral CA3 sends 3–4 times as many backprojections than dorsal CA3 [50,62]. Taken together the

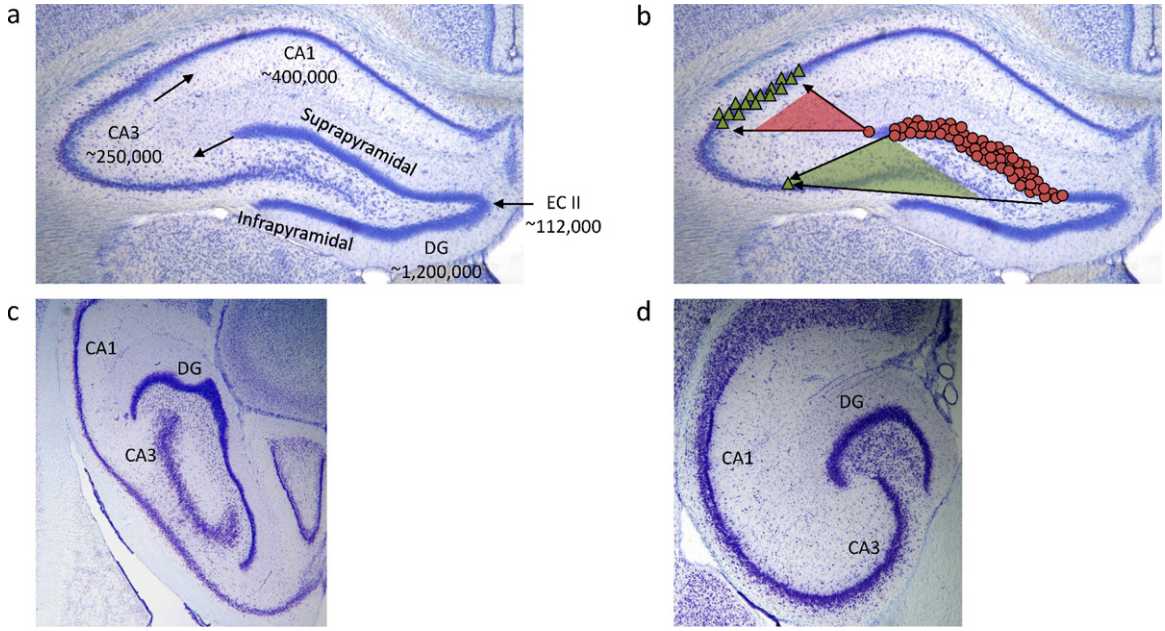

Fig. 1. Coronal section of dorsal hippocampus. (a) The ~112,000 pyramidal cells in EC send divergent input via the perforant path to the ~1,200,000 DG granule cells. Axonal (mossy) fibers from the granule cells converge to innervate the ~250,000 CA3 pyramidal cells. CA3 pyramidal cells innervate the ~400,000 CA1 pyramidal cells via Schaffer collaterals [115]. The DG is composed of the suprapyramidal (enclosed) blade below CA1 and the infrapyramidal (exposed) blade below CA3. (b) The DG is believed to support pattern separation via its scant but powerful connections to CA3 and the probability that an individual CA3 cell will receive inputs from two active granule cells is very low. One granule cell (red circle) targets ~15 CA3 pyramidal cells (green triangle) and each CA3 cell receives convergent input from ~72 granule cells [116]. (c,d) Horizontal section of the dorsal (septal) and ventral (temporal) hippocampus. The ratio of granule cells to CA3 pyramidal cells is greater in the dorsal hippocampus (12:1) than the ventral hippocampus (2:3) [34]. The contact probability of mossy fibers on the CA3 pyramidal cells is also much lower in dorsal hippocampus [6]. Dorsal hippocampus magnification 2×, ventral hippocampus magnification 4×. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

data indicate divergence from the EC and convergence from the DG to CA3 specifically concentrated to the dorsal pole.

1.3. Electrophysiology

Several electrophysiological observations have confirmed the predictions of the pattern separation hypothesis. Very early in the process of theorizing about pattern separation, it was proposed that, in addition to sparse connectivity, granule cells should have a very sparse pattern of activity *in vivo* and have very powerful connections [68]. Subsequent studies have confirmed that a single mossy fiber is capable of acting as "detonator" synapse and firing a downstream CA3 neuron [47]. Moreover, parallel recording of multiple units in freely moving animals have provided observations consistent with the models. Such recordings have shown that granule cells in the DG fire in a spatially selective manner [52,60]. Similar to "place cells" in CA1 and CA3 [77,78], granule cells also exhibit directional firing fields [40,52], are fixed to local and distal references [40], and respond to the novelty of the environment [76]. Interestingly, unlike pyramidal cells in CA1 and CA3, granule cell's exhibit multiple small place fields in a given environment [60].

Single unit recordings also show that the DG may facilitate pattern separation by two (none exclusive) means: sparse firing and remapping. First, orthogonal representations are supported by the sparse firing of granule cells. In CA1 30–40% of cells exhibit place specific firing [77,78]. However, facilitated by the lateral inhibition mediated by cells in the hilus [100], only 2–4% of granule cells are active in any given environment [52,60]. The second process linking the DG to pattern separation is remapping. Remapping is a change in the neuronal representation of an environment in response to alteration of the environment, trajectory taken or changes in cognitive demands [30,31,41,57,58,61,63,79,91,96,99,101,112,117].

The remapping response can be shown by changes in the firing rate of the cells activated in the environment ("rate remapping") or in the population of cells recruited to fire within the environment ("global remapping", for more details see [59]). Whereas global remapping relies heavily on medial EC input [33], rate remapping mechanisms may originate in the DG [110]. Notably manipulations that impaired pattern separation in the DG resulted in impaired rate remapping in CA3 [67].

Theoretical and computational models indicate pattern separation in the DG [85–87]. An elegant study by Leutgeb et al. [60] provided single unit data supporting this idea. Granule cells were recorded from rats traversing similar environments with different spatial contexts (a square and circle environment). The square or circle environments incrementally transformed from one to the other. Granule cells were extremely sensitive to changes in spatial configuration. Granule cells exhibited global remapping between the different environments and gradual changes in firing rates with the incremental changes in the environment. In addition to shape, changes in size or color of the environment were sufficient to induce remapping. Theoretically, pattern separation could originate in the DG or in its cortical afferents [19,88]. However Leutgeb et al. [60] showed that granule cells in DG showed a remapping response even when grid cells in the medial EC (upstream to the DG) did not change their firing patterns.

Thus the single unit data indicate pattern separation occurring within the DG. Remapping was seen in response to an array of physical manipulations of the environment and corresponds with DG connectivity and the behavioral correlates of DG damage. Extracellular recording from individual neurons is technically challenging in the DG since these cells have very low rates of firing and the difficulty in localizing recording sites. Subsequently there are few DG single unit studies. This has left unanswered some fundamental questions regarding DG pattern separation: 1) Given the

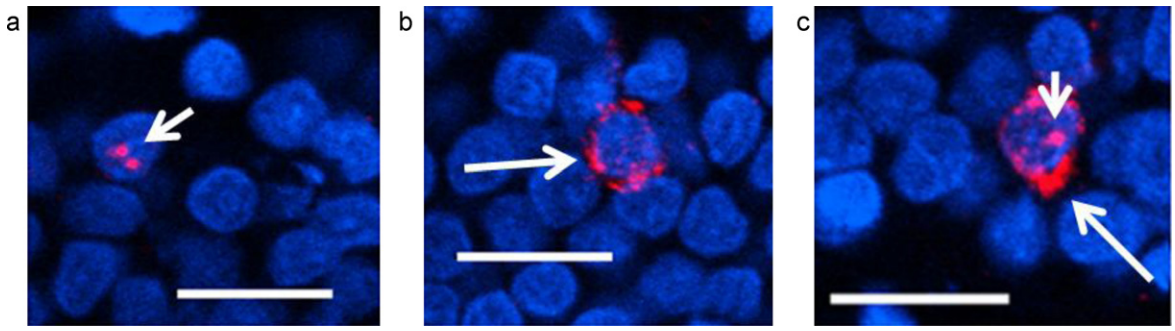

Fig. 2. The compartmental expression of IEGS can be measured to provide a histological record of activity in granule cells. (a) Cellular expression of *zif268* (red) is localized within the nucleus (blue) in cells (short arrow) active five minutes before brain extraction. (b) Cellular expression of *zif268* is localized in the cytoplasm (long arrow) in cells active twenty-five minutes before brain extraction. (c) Granule cells active during both temporal epochs express *zif268* within both cellular compartments (scale bar = 20 μm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

changes in number of granule cells and connectivity to CA3 along the longitudinal axis how does this affect remapping along this axis? 2) What is the relationship between the degree of physical change in the environment and the response in the DG? 3) Does the DG respond only to physical change or also to cognitive/task demands? One way to address these questions and the broader issue of pattern separation is to examine immediate early gene activation (IEG) in the DG under different conditions.

2. New insights on pattern separation in the DG from gene expression

The defining features that make the DG attractive as a seat for pattern separation also make recording the activity of individual DG neurons in this region during behavior challenging. These challenges may be overcome by using IEGs to label granule cell activity. Specifically, cellular compartmental analysis of temporal activity by florescence *in situ* hybridization (catFISH) allows for the "time stamping" of cellular activity by measuring the IEG expression during distinct behavioral epochs [44]. This provides a means to measure the pattern of recruitment of cells into plastic networks of cell assemblies during learning and how that recruitment is affected by change.

2.1. Using zif268 to timestamp granule cell activity

Several IEGs, such as *Arc* and *zif268*, are produced in response to neural activation associated with information processing [15,44], are tightly coupled to cellular activity and are essential for synaptic plasticity [43,51,81]. The expression of both of these IEGs has shown to be a valid indicator of cellular activity in the DG [20,66,92], replicating electrophysiological studies [40,52,60]. These gene products are transcribed immediately and localized to the nucleus and when labeled by *in situ* hybridization a punctate intra-nuclear signal can be observed within five minutes after cellular activity. As these transcripts migrate to the cytoplasm, IEGs accumulate in sufficient numbers to permit a second signal to appear in the cytoplasm following *in situ* hybridization twenty-five minutes after cellular activity. Thus, cellular activity can be mapped during different behavioral epochs within the same rat (Fig. 2) [44]. Although little is known about the firing patterns sufficient to induce IEGs in granule cells during behavior, running a single lap through a track (a single pass through a place field) is sufficient to induce robust IEG expression [72]. Additionally, patterns of stimulation sufficient to induce long-term plasticity reliably induce IEGs, such as *Arc* and *zif268*, and this expression is necessary for plasticity to become long-lasting [51,81].

2.2. DG IEG activation results are similar to single unit recording findings

Studies examining DG cell activity using IEG expression have consistently found sparse activity with the DG, ranging from 2–4% of granule cells in a single context (~2.5% [1]; ~2% [20], ~4% [66], ~4% [92]; Fig. 3a). This proportion of active cells is comparable to the sparse encoding found in single unit studies [40,52,60].

Chawla et al. [20] utilized catFISH to measure *Arc* expression in the DG in rats that traversed two physically distinct environments. Similar to electrophysiological studies, measuring *Arc* expression indicated that distinct ensembles of DG granule cells expressed *Arc* mRNA when a rat visited each environment. However, when the rat traversed the same environment twice the same ensembles of granule cells expressed *Arc*. A follow-up study by Marrone et al. [66] utilized *zif268* expression to timestamp cell activity in the DG. In rats that explored the same environment twice approximately 70% of cells active on one visit were also active on the second. Conversely, when the two environments differed there was only a 35% overlap (Fig. 3b). The data from these two studies indicates that granule cell assemblies are context-specific. That is, significant changes occur in the identity of cells that are recruited in multiple environments, although this overlap is much higher than is seen in other hippocampal regions (discussed further below).

Though IEG expression data agree with the single unit findings it should be noted that the IEG data only indicate cell expression at some point during the session. Other phenomena such as changes in firing rates ("rate remapping"), the development of additional place fields for a single cell, or changes in the location of place fields within a session cannot be differentiated using this method. In other words, IEG data provide a conservative measure of pattern separation since it only provides an index of change in granule cell recruitment.

2.3. Robust responses to small changes

As mentioned, Marrone et al. [66] measured *zif268* expression in rats that explored two environments that differed in spatial and local cues. In response to this dramatic difference between environments, 65% of activated cells showed activation in only one of the environments. However, it was previously unknown as to whether subtle manipulations, such as changes in task demands, affected granule cells ensemble dynamics.

Recently it has been shown that a comparable degree of remapping can be induced by changes in task demands within the same environment (Fig. 3b). In a study by Satvat et al. [92], rats traversed a plus maze twice a day with a twenty-five minute break

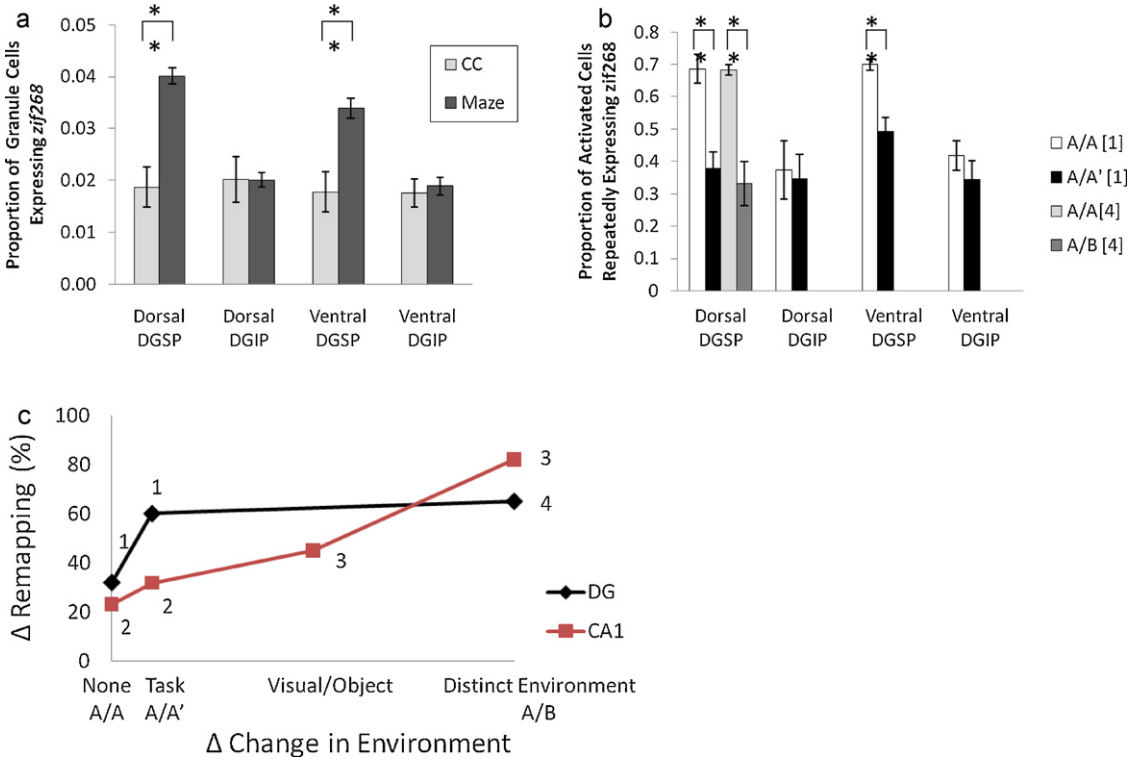

Fig. 3. Granule cell activity and pattern separation. (a) A greater proportion of granule cells express *zif268* in the suprapyramidal (DGSP) blade than the infrapyramidal blade (DGIP) of both the dorsal and ventral DG during spatial exploration. Granular expression of *zif268* is comparable to caged control rats in the infrapyramidal blade. (b) Measuring IEG expression demonstrates that different ensemble of granule cells in the suprapyramidal blade are active (repeatedly expressed zif268/overlap) when placed in two distinct environment (A/B) versus the same environment twice (A/A) during two distinct temporal epochs [66], or when repeating the same navigational strategy (A/A) or two different strategies (A/A') with the same trajectory [92]. When repeating the same task and environment (A/A) ~70% of granule cells in the suprapyramidal blade repeatedly expressed zif268. Both a major change in environment (A/B) and just a change in task (A/A') keeping visual stimuli, trajectory, and motivational states constant, resulted in similar levels of remapping (only about 30% of cells repeatedly expressed *zif*268). In the infrapyramidal blade, no differential recruitment is apparent (*$p < 0.001$: same strategy vs. different strategy within the same region). (c) Comparison of IEG studies suggests that the DG is maximally responsive to small manipulations (such as using different cognitive strategies) or large (physical change in environment). Remapping is comparable regardless of the degree of contextual differences. This is not the case in CA1, where incremental changes in the environment tend to induce progressively more remapping. [1][92]; [2][64]; [3][112]; [4][66].

between sessions. Rats were trained to use either a spatial "place" strategy ("go east") or a motor–response strategy ("turn right") on the same maze. Half the rats performed the same navigational strategy twice (place–place or response–response), half used different navigational strategies (place–response or response–place). During training all start arms were used, however, on the day the brains were extracted the rats ran all trials from the same arm. The behavioral paradigm was designed to maintain identical sensory stimuli, trajectory direction (future and past), velocity, motivation, and environment during the two navigation sessions: the only difference between the two sessions was the strategy that the rats utilized to successfully receive reward during each session. The same cells ensembles repeatedly expressed *zif268* in rats trained to use the same navigation strategy (~65% of granule cells repeated expressed *zif268*). This was not the case in rats trained to utilize two different strategies (switch between place and response navigation). Distinct ensembles of granule cells induced *zif268* (only ~35% of granule cells repeated expressed *zif268*).

A comparison of results among these studies indicates a non-linear or step function response in the DG. Even small manipulations result in changes in ensemble recruitment (Fig. 3c). Regardless of whether contextual manipulations are large, such as physically distinct environments [66], or subtle, such as different cognitive strategies [92], a similar proportion granule cells (~65%) were active in only one of the different tasks/environments. In fact, even when engaging in the same task in the same place on two separate occasions, the probability that the same cell will be active on both occasions is considerably less for granule cells (~0.7, [66]) than for pyramidal cells (>0.9, [44]). Once again the data supports the pattern separation hypothesis: the predisposition for remapping in granule cells in the face of small changes (even over time) are consistent with theoretical ideas for the role of the DG. As noted before, measuring IEG expression gives a conservative estimate of change and it remains possible that remapping is in fact more robust than these data portray, for instance, if more subtle changes such as in firing rate that would differentiate between the two sessions. This final point is particularly relevant when considering some of the data generated recently that are incompatible with the pattern separation hypothesis, discussed in more detail below.

3. Inconsistencies and open questions in the pattern separation hypothesis

As evidence consistent with the pattern separation hypothesis accumulated and the proposed separation function for the DG has increasingly become accepted, a number of outstanding issues remain. There are several areas in which either (a) recent data is inconsistent with the hypothesis, or (b) questions with important ramifications for the hypothesis have yet to be addressed.

3.1. Correlated recruitment of granule cells

While the prediction of sparse activity among granule cells has been confirmed, the population behavior of these cells is not consistent with what the theoretical model would predict. The "classic" notion of pattern separation in the DG presupposes that the

reason that this region has one of the highest cell packing densities in the brain (particularly when this large pool of cells is continually refreshed) is to permit the recruitment of *distinct* granule cell populations in response to different experiences. In contrast, both electrophysiological recordings [1,52,60,97,98] and gene expression data [1,66,92] have consistently shown that a subpopulation of granule cells are predisposed to being repeatedly active in multiple, physically distinct environments. Unlike other regions of the hippocampus in which the probability that a single cell will be active in two environments is approximately equal to random chance with replacement, it seems likely that the distribution of firing thresholds in the granule cell population is highly variable, and those cells with the lowest thresholds are predisposed to become active, regardless of the environment that is experienced. It should be noted, however, that de-correlated input can be accomplished by means other than recruitment of independent populations of granule cells. Ultimately, the de-correlated input would be determined by the population vector (i.e., the instantaneous firing rate of all granule cells in a given location or at a given point in time). It is possible that these vectors may be uncorrelated, even if the population of granule cells recruited is not completely orthogonal. In fact, the data that exist, although scarce, indicate that this is, in fact, what occurs [60]. The "rationale" for having such a high density of granule cells alongside such sparse activity, however, is not clear and the pattern separation hypothesis must account for this effect. This is particularly true given recent data [66] correlating recruitment with memory performance. These data show that the animals that perform *best* at discriminating two highly similar environments (a task that depends on the DG and pattern separation), are those that recruit more of *the same cells* during exposure to both environments. This is the opposite of the prediction by the classic model of DG pattern separation, and suggests that correlated recruitment is, in fact, *beneficial* to pattern separation.

The mixed population of high and low activity threshold cells and the benefits of correlated recruitment have been incorporated into models that attempt to explain the role of neurogenesis (a defining feature of the DG) in pattern separation.

3.2. The role of neurogenesis in pattern separation

There is mounting evidence that the continual production of new neurons makes a substantial contribution to pattern separation. Although adult neurogenesis has long been associated with learning and memory in general (see [24] for review), it is only recently that behavioral experiments have provided evidence for a specific role for neurogenesis in pattern separation. For instance, knocking down neurogenesis impairs performance in tasks requiring discrimination between highly similar stimuli. Animals with reduced neurogenesis (e.g., through focal irradiation or genetic manipulation) develop impairments in tasks that require the discrimination of similar contexts or stimuli from memory. For instance, mice with knocked down neurogenesis exhibit deficits in a delayed nonmatch-to-place task in a radial maze only when they had to distinguish between adjacent arms, but not when the arms were separated. Similarly, mice with reduced neurogenesis are impaired in a location discrimination task under conditions in which the stimuli were close together [22]. In other recent studies, animals that have had neurogenesis knocked down are impaired at discriminating similar contexts in a fear conditioning task [90,111]. Moreover, manipulations that boosts neurogenesis, also improves performance in touch screen location discrimination [23] and contextual fear conditioning [90].

Given these data, several models have proposed to explain the specific role for neurogenesis in pattern separation [3,4,11,12,114]. Aimone et al. [3] suggested that immature granule cells are more active than the overall population in multiple contexts; these young neurons actually *decrease* DG pattern separation in the classical sense and provide "pattern integration" of inputs occurring close together in time. Similarly, other models have also proposed a temporal code by virtue of young neurons yielding different functional populations at different maturation times [2,13]. Related theories propose that newborn neurons provide "high resolution" to memory by providing a dense population of feature-detecting neurons [3].

These models mutually presuppose that granule cells, which are highly excitable, would fire in response to a wide range of stimuli while they are immature, and that as they mature they would exhibit 'selective tuning': that is, fire selectively in response to events (and thus input patterns) that were experienced while the cell was immature. Although an early study suggested that this sort of selective tuning takes place [107], subsequent work [1] has failed to find evidence of such selective tuning. In fact, the pattern of activity seen using both physiological recordings and gene expression are compatible with granule cell 'retirement'. That is, adult generated cells as they mature begin their lives as highly excitable, but rather than becoming selectively tuned to specific stimuli, they become progressively more inhibited, and eventually reach a threshold in which they are virtually silent in response to physiological stimuli. Such a network, with a rolling population of granule cells that are continuously moving along a continuum from hyper-excitability to silence could perform pattern separation (given these dynamics, cell recruitment could code over time rate coding could be used to differentiate contemporaneous memories), this would be qualitatively different from the pattern separation hypothesis as it classically conceived [80]. Although neurogenesis clearly makes a unique contribution to pattern separation, understanding how this is implemented within the hippocampal network needs further research.

3.3. Functional gradients and their implication for pattern separation

3.3.1. The longitudinal axis

As noted above, along the longitudinal axis the ratio of granule cells to CA3 pyramidal cells changes [34]. Behavioral studies also suggest a functional dissociation along the dorsoventral axis, with the dorsal hippocampus supporting spatial processing and ventral hippocampus supporting emotional/fear learning [73]. Additionally, place cell spatial information decreases along the dorsoventral axis [53,54,89]. This parallels the increase in grid field size along the dorsoventral axis in the medial EC [17,45]. Within the DG there is also a gradient for neurogenesis. The rate of neurogenesis in the dorsal pole is almost double that in the ventral pole [102], while cells near the ventral pole may be preferentially recruited during learning tasks [102].

In contrast to changes in the dorsoventral axis of the hippocampus proper, and in the rate of neurogenesis within the DG, the degree of pattern separation remains similar throughout the longitudinal axis of the DG [92]. This was found when the same strategy was used twice (about 35% remapping in both dorsal and ventral) as well as when animals performed two different strategies (~65% and ~50% remapping in dorsal and ventral respectively; Fig. 3b). Taken together, these data suggest that even though the ventral hippocampus may not be as spatially selective as the dorsal hippocampus, the DG maintains different contextual representations of the environment throughout the longitudinal axis. In addition, the relationship between pattern separation and neurogenesis is more complex than currently postulated since areas with increased neurogenesis do not necessarily exhibit more pattern separation (there is a similar disconnect with neurogenesis when comparing the suprapyramidal and infrapyramidal blades – see below).

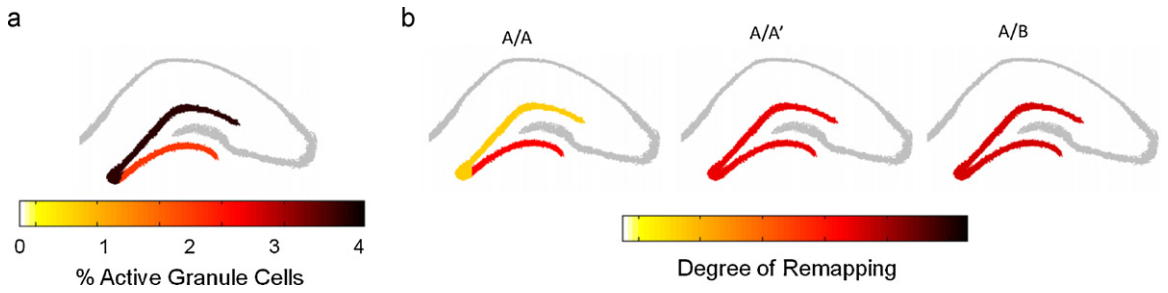

Fig. 4. (a) A greater proportion of granule cells are active in the suprapyramidal blade than the infrapyramidal blade. (b) Measuring repeated activity of IEG expression suggests that a minimal amount of remapping is seen when placed in the same environment (A/A), however, whether the manipulation is subtle, such as using different cognitive strategies (A/A′) or large, such as two distinct environments (A/B), the suprapyramidal blade is maximally responsive. However, the infrapyramidal blade remains constant regardless of the manipulation. Though whether this means the infrapyramidal blade is maximally responsive (recruiting distinct ensemble regardless of the manipulation) or is not sensitive to any differences has yet to be ascertained.

As previously noted, the DG is believed to convey pattern separation via its scant but powerful connections (via mossy fibers) to CA3 [5,68]. However, the gradient of cell density within the DG decreases along the dorsoventral axis and the reverse is seen for CA3 [34]. This may explain the fact that despite the constant level of pattern separation throughout the DG, the relative contribution of the DG to information processing in the CA fields changes along the longitudinal axis [64].

3.3.2. *Function differences between suprapyramidal and infrapyramidal blades*

As mentioned, the DG is divided into the suprapyramidal and infrapyramidal blades (Fig. 1a). Single unit studies typically record in the suprapyramidal blade [40,52,60] preventing a comparison of regions. Mapping suprapyramidal and infrapyramidal cell activity with IEG markers suggest that granule cells in the suprapyramidal blade are more active than in the infrapyramidal blade (Fig. 3a). In fact, in the infrapyramidal blade, *Arc* and *zif268* expression in granule cells is similar regardless of whether the animal traversed the environment or remained in its home cage [20,82,92,113]. Furthermore, both *Arc* and *zif268* demonstrate similar levels of sparse activation in the infrapyramidal blade suggesting that the differences between blades is of overall cell activity rather than unique to a specific IEG.

As noted, granule cells in the infrapyramidal blade do not differentiate traversing an environment from constitutive levels (remaining in the cage). In all cases the activation of the lower blade and degree of remapping is constant (Fig. 3a/b). Thus it appears that the suprapyramidal, but not infrapyramidal, blade is more inclined to exhibit pattern separation in rats that utilized different task demands to solve a maze [92] or traversed different environments [20]. Conversely, these data may indicate extreme sensitivity in the lower blade, with a maximal degree of pattern separation already seen comparing two time windows in the home cage.

The suprapyramidal and infrapyramidal blades are not as homogenous as one might think. During development granule cells migrate first to form the suprapyramidal blade, then the infrapyramidal blade [32]. Granule cells in the suprapyramidal blade have greater dendritic length (3500 μm vs. 2800 μm) and spine density (1.6 spines/μm vs. 1.3 spines/μm) [21,25,26]. There are also differences in cell types and cell density between the two blades. The ratio of granule cells to basket cells in the suprapyramidal blade is 1:100 and 1:180 in the infrapyramidal blade in the dorsal DG. In ventral DG the ratio between granule cells and baskets cells is 1:150 and 1:300 in the suprapyramidal and infrapyramidal blade, respectively [95]. There are also a number of reported connectivity differences between suprapyramidal and infrapyramidal blades. Though a majority of EC layer II pyramidal cells branch off and simultaneously project to the suprapyramidal and infrapyramidal blades [106], projections from medial EC are greater in the infrapyramidal blade and projections from lateral EC are greater in the suprapyramidal blade [103,105]. The suprapyramidal blade preferentially projects to distal CA3 (CA3a) whereas the infrapyramidal blade preferentially projects to proximal CA3 (CA3c), an area reportedly not involved in CA3s auto-associative network [116]. The suprapyramidal and infrapyramidal blades receive inputs from several subcortical regions including the septal nucleus, supramammilary nucleus, locus coeruleus, and raphe nucleus [8]; however, the suprapyramidal blade receives twice as many projections from the supramammilary nucleus [118]. Moreover, neurogenesis (which, as described above, seems to play a key role in pattern separation) shows differences along this axis. There is a higher level of cell proliferation and survival in the infrapyramidal blade than in the suprapyramidal blade [102]. How these differences may explain why the infrapyramidal blade is unresponsive or overly responsive to the environment or task demands is still unclear.

3.4. *The role of hippocampal microcircuits*

Although everything that we have learned to date about how memory is likely implemented within the hippocampus suggest that de-correlated input is critical to hippocampal function, it is not necessary that the DG (uniquely) complete this function. Other microcircuits, including several that partially include the DG granule cell population, have properties that may make them viable alternative candidates as the de-correlators of hippocampal input. For instance, the granule cells of the DG form reciprocal microcircuits with the many cell types of the hilus [18,46,62] as well as with the pyramidal cells in parts of CA3 [50,62,93]. Moreover, there is a small population of granule cells that reside outside the DG and seems to form reciprocal connections with pyramidal cells in CA3 [104]. An exhaustive presentation of these circuits is beyond the scope of this review, and premature, since almost nothing is known about the functional properties of these micro-circuits *in vivo*. This gap in the data is notable, since it is possible that these and other microcircuits may accomplish part or all of the pattern separation function ascribed to the DG.

4. Concluding thoughts

There is convergent evidence linking pattern separation to the DG. Damage to the DG reduces an organism's ability to differentiate between similar objects. The DG has tenfold more principle cells than its cortical input, allowing for a divergence in information flow. Single unit recordings show that DG granule cells have a very different pattern of representing the environment than "classic" place cells in CA1 and CA3, or grid cells in the entorhinal cortex.

The data from IEG experiments have, to a large degree, agreed with and extended on the behavioral and single unit findings. Comparisons of activated populations indicate sparse coding of the environment and distinct populations of cells active when the environment changes. A comparison of IEG studies indicate that the DG robustly differentiates similar situations with even small changes in input inducing a near maximal response in the DG. Interestingly, the DG distinguishes equally well between subtle manipulations within a fixed environment [92], small physical changes [60] and large physical changes in the environment [20,66]. In all cases approximately 65–75% of granule cells were repeatedly active in the same task/environment, but only 35% of granule cells were active in different tasks/environments (Fig. 4). This is not the case for place cells in CA1 which also shown pattern separation in different environments [42,44,57,61,112] and more subtle remapping during different cognitive tasks [64]. This non-linear relationship with environmental change would make sense for a structure whose function is pattern separation.

The two other findings regarding the DG are less intuitive. First, the data indicate that the DG performs pattern separation throughout the longitudinal axis. This finding contrasts findings of dorsal/ventral differences in information processing within the hippocampus proper. Thus the DG can provide pattern separation information throughout the hippocampal formation; however it would seem that the degree to which these changes in the DG impact processing within the hippocampus proper varies along the longitudinal axis. Second, there are differences between the suprapyramidal and infrapyramidal blades of the DG. To date differences in connectivity have been noted but no functional impact has been attributed to these differences. The IEG data suggest a qualitative difference in the processing of information in these two regions.

Conflict of interest

None.

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