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Corruption of the Dentate Gyrus by “Dominant” Granule cells: Implications for Dentate Gyrus Function in Health and Disease

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Abstract

The dentate gyrus (DG) and area CA3 of the hippocampus are highly organized lamellar structures which have been implicated in specific cognitive functions such as pattern separation and pattern completion. Here we describe how the anatomical organization and physiology of the DG and CA3 are consistent with structures that perform pattern separation and completion. We then raise a new idea related to the complex circuitry of the DG and CA3 where CA3 pyramidal cell ‘backprojections’ play a potentially important role in the sparse firing of granule cells (GCs), considered important in pattern separation. We also propose that GC axons, the mossy fibers, already known for their highly specialized structure, have a dynamic function that imparts variance – ‘mossy fiber variance’ – which is important to pattern separation and completion. Computational modeling is used to show that when a subset of GCs become ‘dominant,’ one consequence is loss of variance in the activity of mossy fiber axons and a reduction in pattern separation and completion in the model. Empirical data are then provided using an example of ‘dominant’ GCs – subsets of GCs that develop abnormally and have increased excitability. Notably, these abnormal GCs have been identified in animal models of disease where DG-dependent behaviors are impaired. Together these data provide insight into pattern separation and completion, and suggest that behavioral impairment could arise from dominance of a subset of GCs in the DG-CA3 network.

Keywords

cognition; learning; memory; mossy fibers; hippocampus; computational modeling; ectopic granule cells; addiction; post-traumatic stress disorder (PTSD); estrogen; testosterone

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1. Introduction

Pattern separation and pattern completion are now widely discussed as important functions of the dentate gyrus (DG) and CA3 region of hippocampus. Yet there is also debate – even when defining terms. Here we first review basic structure and definitions for the purposes of this review. Then we discuss some relatively unappreciated aspects of the structure and function of the DG and CA3 that support pattern separation and completion. Finally we use computational modeling and empirical methods to shed new light on pattern separation and completion in health and disease.

1.1. Circuitry of the DG and CA3

Figure 1 provides a simplified schematic of major cell types and connections in the dentate gyrus (DG) and CA3. There are several excellent reviews about the basic circuitry of these areas in rodents and primates (Shepherd, 2004; Andersen et al., 2006; Scharfman, 2007b) including quantitative descriptions of rodent DG, with details regarding cell types, numbers, and connectivity (Morgan et al., 2007). Rodents are the focus here. In Figure 1, several elements of the fundamental circuitry are simplified or collapsed for implementation in a computational model of the DG and CA3 (Myers & Scharfman, 2011; Myers et al., 2013). In brief, the primary glutamatergic input from cortex is the perforant path, formed by axons of neurons of layer II of the entorhinal cortex. The perforant path innervates the distal dendrites of DG GCs in the molecular layer, as well as processes of the GABAergic interneurons (INs) located in that layer. INs are subdivided into those that innervate the GC soma (perisomatic-targeting) and dendrites (dendritic-targeting neurons), with basket cells and axo-axonic cells comprising the former and *hilar* cells with axon terminals in the molecular layer containing the *perforant path projection* (HIPP cells; (Han et al., 1993; Freund & Buzsaki, 1996)) reflecting the latter. Another major cell type is the hilar mossy cell, which is glutamatergic and has projections locally and distally in the DG, primarily to the proximal dendritic layer of the GCs, called the inner molecular layer (Scharfman & Myers, 2012). In area CA3, where the principal cells are pyramidal cells, a similar circuitry exists but without mossy cells. In addition, CA3 pyramidal cells have axon collaterals that innervate each other, called the recurrent collaterals. There also is a ‘backprojection’ from CA3 pyramidal cells to the DG (Figure 1; (Scharfman, 2007b)). Additional complexity exists which is not shown in the schematic, such as additional IN subtypes in the DG (Houser, 2007) and the assumption that principal cells are homogeneous. Rationales for these simplifications are discussed elsewhere (Myers & Scharfman, 2009, 2011; Myers et al., 2013).

1.2 Terminology: pattern separation and completion

As noted above, CA3 pyramidal cell axons form recurrent collaterals that innervate other CA3 pyramidal cells. Numerous computational models have suggested that the high degree of recurrency among pyramidal cells could support memory storage and recall (Marr, 1971; McNaughton & Morris, 1987; Rolls, 1989a, 1989b; Rolls & Treves, 1994; Treves & Rolls, 1994; Kesner, 2007). In this view, input “patterns,” representing activity in a subset of perforant path axons, are stored in CA3 via modifiable synapses between pyramidal cells. The stored pattern is reflected by coactivity in these pyramidal cells, reminiscent of the “cell

assemblies” proposed by Hebb (Hebb, 1949). To store new patterns for later retrieval, most computational models of CA3 assume the presence of so-called “teaching inputs,” inputs that are strong enough to trigger postsynaptic activity and trigger long-term synaptic plasticity between the postsynaptic cell and other coincidentally active presynaptic cells (e.g. from entorhinal cortex). It has long been speculated that the mossy fibers, which form extraordinarily large and strong synapses onto proximal apical dendrites of CA3 PYR, could serve as teaching inputs (McNaughton & Morris, 1987; McNaughton & Nadel, 1990; Treves & Rolls, 1992; Rolls, 1989a, 2007). Empirical support of this idea comes from physiological recordings in which spike trains in a single mossy fiber can cause the postsynaptic CA3 pyramidal cell to reach firing threshold (von Kitzing et al., 1994; Henze et al., 2002; Henze et al., 2002; Kobayashi & Poo, 2004). According to this view, input from the entorhinal cortex via the perforant path targets CA3 pyramidal cells directly and also indirectly via the GC mossy fibers. Sparse activity in GCs means a few GCs spike, and those GCs give rise to mossy fibers that are strong enough to evoke postsynaptic activity in the pyramidal cells they target, allowing synaptic strengthening between those pyramidal cells and coactive entorhinal inputs, storing the pattern. After the storage of a pattern, if a partial or noisy version of the stored pattern is presented, pyramidal cell activity in the previously-strengthened pathways can reinstate or complete the stored pattern, a process termed **pattern completion** (e.g. (Marr, 1971; McNaughton & Morris, 1987; Rolls, 2013)). Empirical data support this idea by implicating the hippocampus, specifically CA3, in behaviors that require recognizing familiar (or partially-distorted) stimuli, and which are therefore assumed to require pattern completion in neural representations (e.g. (Kesner, 2007; Neunuebel & Knierim, 2014)).

In addition to its role as a “teacher,” many prior computational models also propose that the DG pre-processes inputs from the entorhinal cortex by performing **pattern separation**, altering representations of input patterns to make them sparser (containing fewer active elements) and less overlapping (so that elements activated by one input pattern are unlikely to be activated by other patterns) (e.g. (Rolls, 1989a, 1989b)), which facilitates subsequent storage and retrieval in CA3. Recent empirical data support this idea by implicating the DG in tasks that require similar stimuli to be distinguished (Gilbert et al., 2001; McHugh et al., 2007; Hunsaker et al., 2008; Clelland et al., 2009), and which therefore presumably require pattern separation in neuronal representations. To date, a large number of computational models have embodied these basic ideas of pattern storage and pattern completion in CA3, and pattern separation in DG to preprocess information for CA3 (for review, see (Myers & Scharfman, 2011)).

2. Structural and physiological characteristics of the DG and CA3 that support pattern separation and completion

2.1 Anatomical features of the EC-DG pathway

A pattern separation function appears consistent with known quantitative features of the perforant path input to the DG. For example, if one simply considers the estimates for the numbers of entorhinal cortex layer II neurons and the relative number of DG GCs, there are a large number of GCs relative to layer II neurons (Figure 2A; Amaral et al., 1990).

Therefore, one would predict that the anatomical organization will naturally “sparsify” the input from the entorhinal cortex to the DG (Figure 2A; (Rolls, 1989a, 1989b; Rolls & Kesner, 2006; Rolls, 2013). However, a single layer II projection cell has an axon that makes en passant synapses on GCs throughout the superior and inferior blade (Tamamaki & Nojyo, 1993) and GCs receive numerous synapses from different layer II neurons, making the anatomical organization more complex than one would conclude based on numbers alone.

2.2 The role of hilar neurons and backprojections from CA3 to the DG

While the numbers of cells may produce sparse firing of GCs in the spatial domain, GCs also have intrinsic properties that will make it likely that entorhinal cortex input will result in sparse firing in the temporal domain. In other words, a given afferent input will only be able to activate any particular GC for a brief period of time. The characteristic of GCs that is most commonly considered to limit firing is spike frequency adaptation (Figure 2B). This characteristic makes it difficult for neurons to fire repetitively at high frequencies if they are depolarized persistently (Mody et al., 1992; Scharfman, 1992)). Unlike the other cell types in the DG, such as mossy cells and GABAergic neurons, GCs have very strong spike frequency adaptation (Scharfman, 1992; Staley et al., 1992). This characteristic will make it difficult for a given GC that is activated by the entorhinal cortex to be activated repetitively.

A polysynaptic pathway also is present that could potentially silence GCs that were previously active by GABAergic inhibition. This pathway is shown in Figure 2C. In brief, a subset of GCs are first activated by the entorhinal cortex; these in turn activate CA3 pyramidal cells in the same lamella because GC axons are contained primarily in a lamellar plane (Amaral & Witter, 1989). CA3 pyramidal cells have axon collaterals that project back to local INs in the same lamella, which inhibit GCs in that lamella (Figure 2C1; (Scharfman, 2007a)). This pathway would be disynaptic and therefore silence GCs for approximately 10–20 ms after the initial GC action potential, based on recordings in hippocampal slices (Figure 2C4 (Scharfman, 1994b)). In addition, CA3 pyramidal cells innervate mossy cells that activate local INs (Scharfman, 1994a; Scharfman, 1995; Larimer & Strowbridge, 2008). That pathway would silence GCs after a longer delay because there are more synapses involved (pyramidal cell to mossy cell, mossy cell to IN, IN to GC; Figure 2C2). Even longer-duration silencing of GCs could occur if the first pyramidal cell does not project to the DG, but instead innervates another pyramidal cell that does project to the DG (Figure 2C3). Notably, the projections back to the DG do vary across the hippocampal axis, with pyramidal cells in CA3c having greater projections to the DG than those in CA3b (Ishizuka et al., 1990; Li et al., 1994). The net effect of these multiple pathways involving CA3 pyramidal cell ‘backprojections’ is silencing of GCs primarily in the same lamella where the original GCs were activated. This inhibition can silence GCs for a relatively long time period, possibly up to 50 msec, because the inhibitory pathways may be disynaptic, trisynaptic, or even involve more than 3 synapses (Figure 2C4).

At the same time that GCs are silenced in the same lamella where EC-induced activation of GCs originated, GCs will be depolarized in distal lamellae by distal projections of mossy cells. However, the net effects of distal projections is still not clear (Scharfman & Myers,

2012). Nevertheless, overall the backprojections should play an important role in DG function and potentially pattern separation and completion. In support of that idea, deleting backprojections has had major effects in computational models of the DG-CA3 network, where pattern separation and completion are simulated (Myers & Scharfman, 2011; Myers et al., 2013). For example, a computational model of DG-CA3 interactions which includes backprojections is able to perform both pattern completion (retrieving a previously stored pattern, given partial or degraded inputs) and also pattern separation (creating stored patterns in CA3 that are more distinct – less overlapping – than the original entorhinal and DG inputs); when the backprojections are deleted in the model, pattern completion still occurs but pattern separation is degraded (Myers & Scharfman, 2011). As a result, storage capacity, defined as the number of patterns that can be stored and retrieved in the model, is higher when backprojections are present (Myers & Scharfman, 2011). Other computational modeling studies have also found a role of backprojections (Kesner 2013; Krasne et al., 2015; Petrankonakis and Poirazi, 2015).

2.3 “Pre-processing” by the DG: the role of diverse granule cell activation and mossy fiber variance

In addition to simply performing pattern separation, along both spatial and temporal dimensions, the DG may more dynamically pre-process entorhinal cortex information before it reaches CA3. As discussed above, GC axons, the mossy fiber axons, may serve as “teaching inputs” to CA3. But they also have characteristics that impart a large dynamic range or variability in their effects (Scharfman & MacLusky, 2014). For example, mossy fibers release both glutamate and GABA (Jaffe & Gutierrez, 2007), and mossy fiber transmission exhibits numerous types of plasticity, including structural, synaptic, and plasticity of gene expression. When neuronal activity of the GCs is high, neuropeptides such as neuropeptide Y increase expression, which is functionally significant because when released from mossy fibers, neuropeptide Y binds to Y2 receptors on mossy fiber terminals to decrease glutamate release from mossy fibers (Scharfman & Gray, 2006; Sperk et al., 2007). Conversely, the neurotrophin brain-derived neurotrophic factor (BDNF) increases protein expression in mossy fibers in response to high levels of neuronal activity; when BDNF is released it binds to presynaptic trkB receptors to increase glutamate release from mossy fibers (Scharfman et al., 2003). In fact, mossy fiber terminal boutons have many receptors for neuromodulators, possibly more than most boutons in hippocampus (Scharfman & MacLusky, 2014). Thus, the mossy fibers have characteristics that give them the potential to vary their effects widely depending on the recent history of neuronal activity and other neuromodulators released into the region of mossy fiber terminals. We call this variability “mossy fiber variance.”

The potentially diverse range of mossy fiber transmission seems unlikely to be a coincidence. Instead, it could be a critical aspect of the pre-processing of entorhinal cortex input by the DG before it reaches CA3, facilitating CA3 memory function by ensuring that to-be-stored input patterns are made as distinct as possible (i.e. recruiting non-overlapping populations of CA3 pyramidal cells).

In summary, mossy fiber variance could be important to pattern separation and completion. Below we discuss support for the hypothesis that it plays a role in pattern separation and completion, from computational modeling and empirical approaches.

3. Hilar ectopic GCs and their effects on pattern separation and completion

3.1 Hilar ectopic GCs (hEGCs)

In diseases such as temporal lobe epilepsy (TLE), a subset of GCs often develop that are called hEGCs because they are located in the hilus instead of the normal location, the GC layer (Figure 3). Ectopic locations of GCs also may occur in other conditions, because they are found in mouse models of autism, schizophrenia and alcoholism, but most is known from animal models of TLE (Scharfman & McCloskey, 2009).

HEGCs do exist normally, i.e., in normal rodents, but in very small numbers (Scharfman et al 2007). In the normal adult rat, the numbers, based on stereological estimates of a GC marker (Prox1; (Oliver et al., 1993; Liu et al., 2000)) suggest that less than 2,000 hEGCs per hippocampus are present compared to the estimated 500,000–1,000,000 GCs in the GC layer (West et al., 1988; Amaral et al., 1990; West et al., 1991). In the normal adult mouse, the number is no more than 1,000 for the C57bl6 strain (Bermudez-Hernandez et al., 2014). In contrast, there are several pathological conditions that lead to an increase in hEGCs. One example is TLE following an insult or injury. In an animal model of this type of epilepsy, hEGC numbers, again based on stereological estimates, were up to 10x their normal number (McCloskey et al., 2006; Jiao & Nadler, 2007; Hester & Danzer, 2013).

HEGCs in these animals with epilepsy are believed to develop because the initial insult or injury causes a rapid increase in proliferation of progenitors. Some of these progenitors become glia, some die, but many become GCs (Parent et al., 1997). The initial insult is typically induced by administering a convulsant so that severe seizures occur for several hours (status epilepticus). Many genes are upregulated (Lukasiuk & Pitkanen, 2004, 2007) and there is also excitotoxicity of vulnerable hilar mossy cells, HIPP cells, entorhinal cortex and other neurons (Scharfman, 1999; Schwarcz et al., 2002; Sloviter et al., 2003). A similar large increase in proliferation occurs after other types of seizures that induce epilepsy (Mohapel et al., 2004; Koyama et al., 2012).

There are likely to be several ways the rise in proliferation leads to GCs that are located in the hilus. After status epilepticus there is a reduction in reelin-expressing hilar INs and the loss of reelin is considered to block a normal ‘stop’ signal that normally prevents migration to the hilus (Gong et al., 2007). In another animal model of epilepsy, where febrile seizures in young animals are used to induce the epilepsy, mismigration of GCs appears to be induced by disruption of normal GABAergic signaling (Koyama et al., 2012). The normal depolarizing influence of GABA in developing GCs, a very important signal for GCs to migrate to the GC layer, is reduced or lost. As a result, ectopic GCs develop in the hilus. HEGCs can also be produced in mice without seizures, by perturbing the genes that normally are important in development. For example, deletion of *BAX* impairs apoptosis of hilar progenitors during development (Myers et al., 2013). In this case, progenitors that

normally populate the hilar region in early life do not die during development, and persist into adulthood as hEGCs (Bermudez-Hernandez et al., 2014).

Once formed, the axons of hEGCs – which have been studied primarily in animal models of epilepsy - are similar to normal mossy fibers, innervating pyramidal cells in CA3 with complex ‘giant’ boutons (Pierce et al., 2005). In both the BAX knockout mouse and epileptic rat, hEGCs are more likely to fire action potentials spontaneously than normal GCs (Scharfman et al., 2000; Myers et al., 2013), possibly because of drive from CA3 pyramidal cell backprojections (Scharfman et al., 2000; Scharfman, 2007) and a resting potential that is closer to threshold than granule cell layer GCs (Zhan & Nadler, 2009; Zhan et al., 2010; Althaus et al., 2014). HEGCs also receive more excitatory drive from mossy fibers of granule cell layer GCs, presumably due to their location in the hilus (Scharfman et al., 2000; Pierce et al., 2005). Therefore, hEGCs become a subset of GCs that are more active than GCs in the GC layer (Figure 3).

3.2. Effects of hEGCs in a DG-CA3 computational model

To explore the effects of hEGCs on pattern separation and completion, hEGCs were incorporated into our preexisting DG-CA3 computational model (Myers & Scharfman, 2011; Myers et al., 2013). If even a fairly small number of GCs were hEGCs in the model, the effect was to decrease the ability of the model to perform pattern separation and completion (full modeling details are provided in (Myers et al., 2013). Specifically, Figure 4 compares a ‘Standard’ DG-CA3 model, with all GCs placed in the GC layer, and a ‘New’ model, where a small proportion (5%) of GCs were placed in the hilus and made slightly more excitable than GCs in the granule cell layer, by reducing firing threshold from 0.75 mV to 0.7 mV. For comparison, we also considered an ‘Intermediate’ model with 5% of all GCs made more excitable but placed normally in the GC layer (Figure 4A). Results showed that, while adding a small number of hyperexcitable neurons had very little effect, the effect of an equivalent number of these cells, placed ectopically in the hilus, was profound. For example, Figure 4B shows simulation results when the models were trained with varying numbers of input patterns presented as entorhinal cortex input; the input patterns were randomly constructed so that correlation between pairs of patterns was low (Pearson’s $r < 0.1$ on average). Correlation, measured at the DG outputs (GC axons; Figure 4B1) or CA3 outputs (pyramidal cell axons; Figure 4B2), was low in the Standard model, although it rose slowly as number of trained patterns increased. Similar behavior was observed in the Intermediate model, which did not differ significantly from the Standard model ($p > 0.500$). Thus, the mere presence of a small number of modestly hyperexcitable GCs in the granule cell layer did not disrupt pattern separation. However, the average correlation in both the DG and CA3 was much higher in the New model than in either of the other two models (both $p < 0.001$), indicating a failure of pattern separation when hEGCs were present.

Figure 4C compares pattern completion in the three models. Here, the models were first trained on randomly-constructed input patterns, and then tested with “partial” versions of these trained patterns, in which 0–90% of active elements were deleted (% degradation). Pattern completion was inferred if the pattern of CA3 outputs was closer to the original pattern than to any other trained pattern. Figure 4C1 shows that, when the number of stored

patterns was low, both the Standard and Intermediate models did a good job of retrieving the correct pattern, even when a large part of the pattern was degraded (high % degradation); in contrast, the New model retrieved the correct pattern only about half the time, even when % degradation was low. Thus, even on this fairly simple task, the New model performed worse than the other models ($p < 0.001$), but the Standard and Intermediate models did not differ from each other ($p > 0.200$). When the number of stored patterns was increased from 10 to 50 (Figure 4C2), all models were impaired as % deletion increased (all $p < 0.001$), but whereas the Standard and Intermediate models did not differ ($p > 0.200$), the New model was again significantly worse than both (all $p < 0.001$). In summary, although the presence of a small number of modestly hyperexcitable (“immature”) GCs in the granule cell layer did not significantly impair performance, the presence of the same number of hEGCs significantly impaired both pattern separation and completion in the computational model.

4. The “dominant GC” hypothesis

Given the adverse effects of hEGCs in the computational model (Figure 4), the next question was how hEGCs exerted their effect. One hypothesis that emerged was that hEGCs dominated the activity of the entire GC population – including GCs both in the GC layer and also in the hilus.

The modeling data that led to this idea are shown in Figure 5. In the Standard model, a small percentage (about 2%) of mature GCs fire in response to input from the perforant path. In the Intermediate model, where 5% of GCs in the granule cell layer are immature GCs, some of the immature GCs fire in response to perforant path input, but the percentage of mature GCs that are active does not significantly change from that observed in the Standard model (t-test, $p > 0.500$). In the New model, where 5% of GCs are hEGCs, these hEGCs are dominant, reflected in much higher firing rate of hEGCs relative to mature GCs in the granule cell layer ($p < 0.001$), and a reduced firing rate of mature GCs compared to the Standard model ($p < 0.05$).

The high level of hEGC firing in the New model was primarily due to the location of cell bodies outside the granule cell layer, where they were less subject to influence from interneurons that normally provide somatic and dendritic inhibition to mature GCs in the granule cell layer. As the hEGCs became active, they in turn excited interneurons that helped silence other GCs in the lamella, making it harder for the mature GCs to reach firing threshold. Thus, in the New model, the dominant hEGCs were not only highly active themselves, but appeared to suppress activity in other non-dominant GCs. This led to reduced variance in the GC output (mossy fibers) to CA3, since most entorhinal cortex input patterns produced activity in the same, small group of hEGCs. This in turn impaired pattern completion in CA3, as seen in Figure 4C.

By contrast, when the immature cells were placed in the granule cell layer (Intermediate model), they showed comparable levels of firing to mature GCs, and there was no reduction in firing of the mature GCs. This is because, although the immature cells in the granule cell layer were slightly more excitable in the Intermediate model (due to a slight reduction in firing threshold compared with mature GCs) these immature GCs were still subject to

somatic and dendritic inhibition due to their placement in the granule cell layer. Therefore, they did not become nearly as dominant as hEGCs in the New model.

The implication of this modeling work is that DG-CA3 function is normal when GCs have distributed activity, with no one subgroup of GCs firing more than others. However, when a subset of GCs becomes more active than others, such as hEGCs, function is impaired. One reason for reduced function would be that the dominance of a subset of GCs would lead to repeated targeting of the same subset of pyramidal cell in CA3. In turn, these pyramidal cells become more active than others. If the synapses between these dominant GCs and pyramidal cells were strengthened over time, which would be likely given the robust synaptic plasticity at their synapses, their dominance over other GCs and pyramidal cells would become long-lasting. Furthermore, if a subset of CA3 pyramidal cells were most active, the pyramidal cells they innervate would become more active because of recurrent collateral synapses between them. Ultimately entorhinal cortex input would primarily activate a small fraction of the available GCs and pyramidal cells, impairing both pattern separation, and pattern completion. This hypothesis, the ‘dominant’ GC hypothesis, is diagrammed in Figure 6.

4.1. Dominant GCs in the computational model

To begin to explore this hypothesis further, we began with the Standard DG-CA3 model, and created a small population of dominant GCs in the granule cell layer (see Appendix for simulation details). Here, rather than adding hEGCs, we randomly selected 5% of the granule cell layer GCs to be “dominant GCs,” by reducing their firing thresholds sufficiently to ensure that they would be very likely to respond to any entorhinal cortex input, even in the presence of normal inhibitory processes in the granule cell layer. Thus, “normal” GCs had a fairly high threshold to produce action potentials (e.g. resting potential = -0.30mV , firing threshold = $+0.75$ in the Standard model), whereas dominant GCs were assigned a very low firing threshold of $+0.05$ (“weakly” dominant), so that about 25% would fire in response to any entorhinal input (Figure 7), roughly similar to the activity of the hEGCs shown in Figure 5. We also considered a more extreme model where dominant GCs were assigned an even lower firing threshold of 0.0 (“strongly” dominant), so that they all would respond to virtually any entorhinal input. While there are other mechanisms that could be instantiated to produce dominant GCs within the granule cell layer, this approach ensured that a subpopulation of GCs would be much more likely than other GCs to fire in response to perforant path activity, while not significantly suppressing activity of the remaining non-dominant GCs.

Thus, as shown in Figure 7, about 2% of non-dominant GCs in the Standard model fire in response to perforant path input, and this proportion does not differ significantly in the Weakly-dominant model (t-test, $p>0.500$). In the Strongly-Dominant model, there is actually a slight increase in firing of non-dominant GCs, compared to the other two models (both $p<0.002$), although the effect size is small ($<3\%$ of non-dominant GCs fire in any of the models). However, in the Weakly-dominant model, significantly more dominant than non-dominant GCs fire ($p<0.001$), and this effect is even greater in the Strongly-dominant model ($p<0.001$) where all dominant GCs fire in response to any perforant path input (Figure 7).

4.2. Dominant GCs impair pattern separation and completion

Even though Figure 7 shows that addition of dominant GCs to the model did not appreciably change overall activity levels in the remaining GCs, there was an effect on pattern separation and completion. Figure 8A shows that pattern separation was mildly impaired in both the DG and CA3 when weakly-dominant GCs were present, reflected as an increased correlation in the responses to pairs of entorhinal cortex input patterns; the impairment was considerably more severe when strongly-dominant GCs were present. These impressions were confirmed by ANOVA. Specifically, in the DG, there was a significant effect of model ($F(2,108)=5070.47$, $p<0.001$) with no effect of number of trained patterns ($F(3,108)=1.63$, $p=0.187$), while there was also an interaction between model and number of patterns ($F(6,108)=10.17$, $p<0.001$); post-hoc tests confirmed that the Standard model outperformed the Weakly-dominant model, and both outperformed the Strongly-dominant model, at each number of trained patterns (all $p<0.001$). In CA3, there were main effects of both model ($F(2,108)=347.78$, $p<0.001$) and number of trained patterns ($F(3,108)=20.43$), as well as an interaction ($F(6,108)=18.15$, $p<0.001$). Post-hoc tests revealed that the Standard model outperformed the Weakly-dominant model when 50 or 100 patterns were trained (both $p<0.001$) but not when only 10 or 20 patterns were trained (both $p>0.200$). However, both the Standard and Weakly-dominant models outperformed the Strongly-dominant model regardless of number of patterns trained (all $p<0.001$).

Similarly, there was a modest decrease in pattern completion when weakly-dominant GCs were present (Figure 8B), and a severe decrease when strongly-dominant GCs were present. Specifically, when the number of stored patterns was low (e.g. 10 stored patterns, Figure 8B1), ANOVA revealed a significant main effect of model ($F(2,270)=2179.61$, $p<0.001$) with no effect of test pattern degradation ($F(9,270)=12.54$, $p=.135$) but a model-degradation interaction ($F(18,270)=2.57$, $p=0.001$); post-hoc tests at each level of test pattern degradation revealed that, at all levels tested, the Strongly-dominant model was worse than either the Standard or Weakly-dominant models (both $p<0.001$), which did not differ ($p>0.200$). But when the number of stored patterns was higher (e.g. 50 stored patterns, Figure 8B2), there were significant effects of both model ($F(2,270)=70.80$, $p<0.001$) and percent deletion ($F(9,270)=12.74$, $p<0.001$), with no interaction ($F(18,270)=1.60$, $p=0.060$). Specifically, while performance in all models remained relatively constant for degradation from 0% up to 60% (all $p>0.500$), but declined thereafter, the Standard model outperformed the Weakly-dominant model ($p<0.001$) and both outperformed the Strongly-dominant model (all $p<0.001$). Together these modeling data provide support for the hypothesis that dominant GCs and mossy fiber variance are important determinants of CA3 function.

We have discussed only two of the several ways that dominant GCs could develop: the presence of a population of hEGCs, and the presence of a subpopulation of granule cell layer GCs with very low thresholds; in both cases the result is a reduction in variability of mossy fiber input to CA3, resulting in impaired CA3 memory function, assessed both as pattern separation and pattern completion. It is interesting to consider whether reducing mossy fiber inputs to each pyramidal cell would have a similar effect as dominant GCs. This appears to be the case based on a previous study (Cerasti and Treves, 2010). However, different effects may develop depending on how mossy fiber synapses are reduced. For example, if mossy

fibers are reduced because individual granule cells are lost (perhaps due to injury/disease), one would predict a similar effect as making a subset of GC dominant because one subset of GCs (those that are lost) would be greatly reduced in their contribution to the GC population compared to the residual GCs (which would become analogous to dominant GCs). Future studies would be valuable to evaluate the consequences of changes to the mossy fibers.

5. Dominant GCs, mossy fiber variance, and their implications

Pattern separation and completion are both straightforward to assess via similarity metrics in a computational model. Specifically, pattern separation is defined as decreased correlation or overlap in two input patterns across a population of neurons and pattern completion is defined as how closely a retrieved pattern matches the stored original. Thus, as in Figures 4 and 8, we can simply calculate average correlation or percent similarity across input and output patterns in the model. However, these metrics cannot generally be measured *in vivo*. Instead, they are typically inferred based on behavioral tasks. Thus, animals can be challenged to discriminate similar objects or locations, which presumably invokes pattern separation, or they can be challenged to generalize learned responses when presented with partial versions of familiar stimuli, which presumably invokes pattern completion functions. In fact, putative pattern separation tasks are disrupted when the DG is damaged or dysfunctional (Yassa & Stark, 2011a,b; Husaker & Kesner, 2013; Jackson, 2013; Swan et al., 2014; Neunuebel & Kneirim, 2014) while putative pattern completion tasks are disrupted when CA3 is damaged or dysfunctional (Yassa & Stark, 2011a,b; Hunsaker & Kesner, 2013; Jackson, 2013; Neunuebel & Kneirim, 2014). However, because such empirical data provide only indirect evidence, computational models of these brain structures can help bridge the gap between theoretical information-processing constructs and observed behaviors. Further, computational models provide a method for examining the effects of deleting or manipulating specific network elements – such as addition of hEGCs, modification of firing thresholds in a subpopulation of GCs, or selective deletion of CA3 backprojections – under tight experimental control and in ways that are not technologically feasible in the substrate. Nevertheless, a model is only valid to the degree that it accurately and parsimoniously describes empirically-observed phenomena, and only useful to the degree that it makes novel predictions that can be tested empirically.

In the case of the current work, the model predicts that when a population of strongly or weakly dominant GCs is present, GC firing patterns may be altered and pattern completion and separation functions will degrade. We turn next to discuss some pathological conditions in which dominant GCs may arise, and whether the effects of these dominant GCs are consonant with model predictions.

5.1 Multiple types of dominant GCs in the normal brain

The modeling work presented above suggests that, in addition to hEGCs, a small population of strongly or weakly dominant GCs in the granule cell layer can negatively impact pattern separation and pattern completion. There are several potential examples of such dominant GCs in the literature.

One example could be “semi-lunar” GCs, which are a type of GC that is situated at the border of the GC layer and molecular layer (Larimer & Strowbridge, 2008, 2010). Semilunar GCs have very large, prolonged depolarizations in response to perforant path input, unlike other GCs. The mossy fibers of semilunar GCs strongly activate hilar neurons (Williams et al., 2007; Larimer and Strowbridge, 2008, 2010; Gupta et al., 2012), so their prolonged depolarizations lead to prolonged activity in hilar neurons, similar to “up states” (Larimer and Strowbridge, 2008; 2010). That finding is potentially very important because of the role of cortical up states in working memory; semilunar GCs could be a critical part of the circuitry from cortex to DG during working memory (discussed further in Larimer and Strowbridge 2008, 2010).

Adult-born GCs could be considered another potential subset of GCs that might have a dominant role in the DG network, particularly when they are approximately 4–6 weeks old and have a strong influence on behavior (Alme et al., 2010; Sahay et al., 2011; Gu et al., 2012; Kim et al., 2012; Nakashiba et al., 2012). The effects of adult-born GCs that have been reported are robust compared to their relatively small numbers, approximately 6% of the entire population of GCs (Cameron & McKay, 2001), supporting the idea that they become a type of dominant GC. Interestingly, adult-born GCs have been implicated in pattern separation. Thus, for example, deletion of adult-born neurons using focal low-dose irradiation or transgenic methods impairs the ability to discriminate small differences in images or differences in two adjacent arms of a radial arm maze (Clelland et al., 2009). Conversely, increasing adult neurogenesis 3–4 fold by deletion of the pro-apoptotic gene BAX in nestin-expressing progenitors improves these behaviors (Sahay et al., 2011).

Therefore, in this case the addition of a dominant type of GC may improve rather than have adverse effects. One explanation is that, although dominant, adult-born GCs add variance to the DG output. This idea is based on empirical data showing that activation of adult-born GCs selectively, using optogenetics, causes both inhibition and excitation of other GCs (Drew et al., 2013). Previous studies also have shown that during maturation, adult-born GCs display a dynamic set of intrinsic and synaptic characteristics that make them vary their role in the DG-CA3 circuitry (Dieni et al., 2013; Temprana et al., 2015).

5.2 Epilepsy

In pathological conditions, another subset of GCs besides hEGCs could become dominant. For example, in rodents models of TLE, a fraction of GCs in the GC layer develop basal dendrites that enter the hilus and receive a greater degree of excitatory input than inhibitory input, based on electron microscopy (Thind et al., 2008). It has been suggested that these neurons play a facilitatory role in seizure generation (Ribak et al., 2012), like hEGCs. They also may contribute to co-morbidities of epilepsy such as depression (Ribak et al., 2012). Another subset of GCs can develop an unusual orientation (Murphy et al., 2012) or hypertrophy (Pun et al., 2012).

It is interesting to consider that these aberrant GCs become dominant GCs and this leads to less variance in the mossy fiber pathway to CA3. The outcome would have adverse effects on pattern separation and completion, consistent with the impairments in behavior observed in the rodent models of TLE (Muller et al., 2009; Kandratavicius et al., 2012; Pearson et al.,

2014; Stafstrom, 2014). Dominant GCs may also exacerbate seizures by creating a pathway that has a lower threshold for activation. The lower threshold might develop because the aberrant GCs have intrinsic properties that lead to increased excitability (Althaus et al., 2014), or have a greater ratio of excitatory afferent input relative to inhibitory input (Zhan et al., 2010) like the dominant GCs in Figure 6B. In addition, the synapses onto CA3 pyramidal cells may undergo LTP more readily in the epileptic brain because the threshold for synaptic plasticity is lower, in general, in animal models of epilepsy (Lopantsev et al., 2009; Muller et al., 2013). The outcome would be an easily activated pathway for seizures to propagate through hippocampus. Consistent with these ideas, ablating adult-born GCs led to a reduction in seizures in an epilepsy model, and a normalization of performance in behavioral tasks such as novel object location (Cho et al., 2013).

5.3 Pathological plasticity

Dominant GCs may also play a role in maladaptive plasticity which has been suggested to occur in post-traumatic stress disorder (PTSD) and addiction. One reason to consider PTSD is that it has been described as a disorder where a memory is recalled too easily or triggered by too many cues, even cues that are not clearly associated with the memory itself. In this case, a stored memory – one associated with the trauma that triggered PTSD - may be too easily retrieved from CA3. This might occur if dominant GCs develop and these GCs respond indiscriminately to input from entorhinal cortex, so that the same subset of CA3 pyramidal cells – namely, those encoding the traumatic memory – are repeatedly activated in response to a wide range of inputs. Interestingly, it has been suggested that abnormalities in adult neurogenesis in the DG could underlie pattern separation deficits and lead to anxiety disorders or PTSD (Khierbek et al., 2012). The authors suggested that impairments in adult-born neurons would lead to overgeneralization, with similar cues leading to the same rather than different memories. Dominant GCs would have such an effect.

Another view of PTSD is that pattern completion is highly effective even when there is presentation of incomplete or even erroneous cues. In this case, a stored memory in CA3 could still be retrieved – again the memory associated with the trauma that triggered PTSD - if entorhinal inputs easily trigger a pathway to the pyramidal cells that are involved in storage of that memory via dominant GCs.

Addiction could involve similar pathology – a condition where even a few cues retrieve a maladaptive memory. In this case, the memory of the pleasurable drug-related experience is stronger and more easily-retrieved than other memories relating to negative consequences of continued drug use, contributing to repeated addictive behavior (Kalivas and Volkow, 2005; Kauer and Malenka, 2007; Kalivas and O'Brien, 2008; Koob and Volkow, 2010). The DG-CA3 is potentially implicated because the context or environment often triggers the return to addictive behavior, and the DG has been implicated in the ability to use contextual information. A role in context has been suggested based on experiments showing that DG lesions reduce contextual fear conditioning but not cued conditioning (LeDoux et al., 1990; Phillips et al., 1992; Anagnostaras et al., 1999; Daumas et al., 2005). Thus, entorhinal inputs that normally would not lead to memory retrieval without additional cues might do so in a

DG-CA3 circuit where a pathway from dominant GCs to dominant pyramidal cells is too strong.

5.4 Implications for hormonal modulation of hippocampal function

The idea of dominant GCs and reduced mossy fiber variance provides potential insight into recent studies of androgen regulation of hippocampal function in male rats. In these experiments, mossy fiber synaptic transmission was compared in male rats that had been gonadectomized or received sham surgery (Skucas et al., 2013). The comparison showed that there was greater mossy fiber transmission and mossy fiber LTP after gonadectomy. In addition, mossy fibers lost their spatial selectivity for stratum lucidum, caused by mossy fiber sprouting from stratum lucidum into the pyramidal cell layer and stratum oriens (Figure 9A). As a result, the afferent specificity of mossy fiber transmission was reduced (Figure 9B). These data suggest that normally androgens restrict mossy fiber transmission and plasticity, keeping mossy fiber axons within a specific range and spatial location (Skucas et al., 2013; Scharfman & MacLusky, 2014). Restricting the spatial location of mossy fibers might be critical to normal function, and restricting plasticity might be the 'price' paid to preserve spatial organization. Others have also suggested that there is a 'cost' to high testosterone levels, more generally (Lucion et al., 1996).

Mossy fiber variance also appears to be modified by 17β -estradiol, based on studies of intact female rats at different stages of the estrous cycle. During the time of the estrous cycle when 17β -estradiol levels are high (mid-morning of proestrus) there is a very large variance in mossy fiber transmission and plasticity, with some rats showing increased synaptic transmission, sometimes epileptiform activity, yet other rats not showing the effect (Scharfman et al., 2003). In proestrous female rats, 25% showed an increase in mossy fiber excitability on proestrous morning, an effect of 17β -estradiol (Scharfman et al., 2007). Data were highly variable, but less so at other cycle stages when serum levels of 17β -estradiol were lower (Scharfman et al., 2003). Although these data might be variable for technical reasons, another perspective is that 17β -estradiol is designed to increase mossy fiber variance in the DG-CA3 network because that variance may improve its function.

Returning to the gonadectomized male rat, the effects of androgens may also modify mossy fiber variance; here, androgen may normally reduce variance and limit function. One possible explanation is that in dominant male rats, where androgen levels in the serum are high ((Lucion et al., 1996; Clarke & Faulkes, 1998; Lofgren et al., 2013) see also (Albert et al., 1986)), behavioral plasticity may be less important than it is for the subordinant male, where serum levels of androgen are substantially lower, and animals need to modify behavior to safely obtain food and water. Indeed, in some species of birds the males with higher testosterone levels breed normally but the males with lower testosterone levels develop alternative reproductive behavior (Fagundes et al., 2012).

6. Summary

There is still much to be clarified about the anatomical substrates for pattern separation and pattern completion in the DG and CA3, but there are already some characteristics that are known which are likely to contribute. Here we highlight the potential importance of

backprojections to hilar neurons, but other examples exist. Computational models initiated the first discussions of pattern separation and completion in the DG, and continue to contribute. Here we suggest that diversity of GC activity and mossy fiber variance are important characteristics to maintain these functions. In disease these characteristics may become reduced by the emergence of dominant GCs, such as hEGCs. In addition, we propose that neuromodulation of DG-CA3 function by gonadal hormones may also act by modifying mossy fiber variance.

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Appendix: Simulation Details

DG-CA3 Network: Standard Model

The Standard model follows that of Myers & Scharfman (2013); full implementation details are provided there. In brief, the model includes 10 simulated lamellae. In the DG, each lamella contains 100 GC, 1 interneuron, 3 mossy cells, and 1 HIPP cell. In CA3, each lamella contains 30 pyramidal cells and 1 interneuron. Perforant path inputs are simulated as a vector of 200 axons, each of which can be 1 (“active” or “firing”) or 0 (“inactive” or “not firing”). A “trial” begins when a new subset of perforant path inputs are activated, and this pattern (an “input pattern”) is presented to the DG and CA3; the trial ends with a readout of the responses of GCs and pyramidal cells to that input pattern. The responses of GCs and pyramidal cells are designated as either suprathreshold (an action potential, output=1) or subthreshold (no action potential; output=0). There are two output patterns, one representing DG output, which is a vector of 0’s and 1’s representing the action potentials produced by the GCs, and one representing CA3 output, which is a similar vector representing the action potentials produced by the pyramidal cells.

At the start of each simulation run, a new set of DG cells is constructed; in the Standard model, all GCs are placed in the granule cell layer and are designated as “mature GCs.” Mature GCs g have a firing threshold $\Theta[g]=0.75$ and resting potential $V_{rest}[g]= -0.3$. A new set of CA3 cells is also constructed, including pyramidal cells c , which have $\Theta[c]=0.5$ and $V_{rest}[c]= -0.3$. Next a connectivity matrix is formed specifying weighted connections between cell types in DG and CA3; this matrix is based on anatomical details observed in rats (full details given in Myers & Scharfman, 2013) and is as schematized in Figure 1A.

During a simulation run, a specified number (N_{pat}) of input patterns are generated, each with a specified percentage (or density, d) of elements that are active (1) with the remainder inactive (0). In the simulations reported here, the DG-CA3 model is given 5 training passes through the set of N_{pat} input patterns. During each training pass, for each pattern p , the corresponding values are presented as perforant path inputs to the DG and CA3 networks.

In the DGs, GCs become active as a weighted sum of presynaptic inputs from the perforant path. GCs excite interneurons, which then feed back to inhibit GCs in the same lamella, so

that all but the most strongly active GCs are silenced. Mossy cells also receive input from GCs in the same lamella and also from CA3 pyramidal cells via the backprojection; mossy cells then project to a subset of GCs (outside the lamella). HIPP cells receive inputs from the perforant path, mossy cells in the same lamella, and CA3 pyramidal cells in the same lamella, and project back to inhibit GCs in the same lamella. After summing all excitatory and inhibitory influences, each GC g fires (produces output=1) if net activation, passed through a sigmoidal function, exceeds that cell's firing threshold; otherwise the GC does not fire (produces output=0). The vector of output values is the external output of the DG network (the mossy fibers) to the current pattern of perforant path inputs; these project to the CA3 network and are also used to assess pattern separation, etc., in the DG network.

The CA3 network can be operate either PATTERN STORAGE mode, when mossy fiber afferents from the DG are enabled and function as forcing or teaching inputs, or PATTERN COMPLETION mode, when mossy fibers are silenced but recurrent collaterals among pyramidal cells are enabled. In either mode, when a perforant path input is presented to CA3, each pyramidal cell computes weighted activation, according to the connectivity matrix. If the network is in PATTERN COMPLETION mode, then recurrent collaterals from other pyramidal cells also provide excitatory input. Otherwise, if the network is in PATTERN STORAGE mode, then mossy fibers from DG GCs provide strong (teaching) input to CA3 pyramidal cells; input from a single mossy fiber is generally sufficient to cause a pyramidal cell to fire. Next, the interneurons in each lamella become active, based on both pyramidal cell activity within the same lamella and also mossy fiber input to the interneuron (if in PATTERN STORAGE mode); the interneuron then feeds back to inhibit pyramidal cells in the same lamella, so that less-active pyramidal cells are silenced. Finally, each pyramidal cell fires (produces output=1) if its net activation, passed through a sigmoidal function, exceeds the firing threshold; otherwise the pyramidal cell does not fire (output=0). The vector of pyramidal cell outputs forms the backprojection to the DG network and is also used to assess pattern completion, etc., in the CA3 network. In PATTERN STORAGE mode, synaptic weights in CA3 are then modified, using a rule that approximates observed mechanisms of synaptic plasticity (i.e., weights between pairs of coactive CA3 pyramidal cells, or between coactive perforant path inputs and CA3 pyramidal cells, are strengthened

DG-CA3 network: Weakly-Dominant and Strongly-Dominant Models

To create a population of dominant GCs in the granule cell layer (e.g. Figure 6B), we selected at random 5% of all GCs in each lamella, and lowered the threshold from the "standard" value of $\Theta[g]=0.75$ to a value of 0.05 (Weakly-Dominant model) or 0.0 (Strongly-Dominant model). These values were selected to produce activity levels of about 25% GC firing in response to an entorhinal input in the Weakly-Dominant model, or about 100% of GC firing in the Strongly-Dominant model. All other features of these GCs, and all other cells in the model, were the same as in the Standard model.

Assessing Pattern Separation and Pattern Completion

Once a set of patterns is trained, a pattern separation test may be performed (e.g. Figure 4B and 8A). Here, each pair of trained patterns p and q is applied in turn as input to the DG

network, and the output from the GCs to p and q are noted as vectors $R[p]$ and $R[q]$, respectively. Note that $R[p]$ and $R[q]$ each consist of 1000 binary values, specifying whether the 1000 GCs produce output 0 or 1 in response to p and to q . These vectors can be compared via Pearson's r , with lower values indicating better pattern separation in DG (low similarity between patterns). The output from CA3 to each pattern (run in PATTERN COMPLETION MODE) forms analogous 300-bit vectors $R[p]$ and $R[q]$ which specify whether each CA3 pyramidal cell produces output 0 or 1 in response to p and q , and which can be compared the same way to assess pattern separation in CA3.

Alternatively, a pattern completion test may be performed (e.g. Figures 4C and 8B). Here, for each trained pattern p , the CA3 network runs (in PATTERN COMPLETION mode) and the output from the pyramidal cells to p are noted as a vector $R[p]$. Next, for each trained pattern p , 10 "distorted" versions p' are generated that vary from p by setting a fixed percentage (0%, 10% ... 90%) of the active elements in p to 0.

Each distorted pattern p' is then presented to CA3 which produces output $R[p']$. The overlap between $R[p]$ and $R[p']$ is defined as the number of bits with the same value (i.e., the number of pyramidal cells that produce the same output to both p and p'). If the overlap between $R[p']$ and $R[p]$ is greater than the overlap between $R[p']$ and the response $R[q]$ to any other stored pattern q , then the CA3 network has correctly performed pattern completion.

For Figures 5 and 7, the results reflect one representative simulation run for each type of model shown. In Figures 4 and 8, each value in the graphs represents the mean of 10 simulation runs. Simulation results vary from run to run because there are differences in initial conditions - specifically the connectivity matrix and the exact sequence of the trained patterns. Thus, results are presented as a mean with a standard error of the mean, which represents the expected degree to which results vary across simulation runs. Results are analyzed by mixed ANOVA with post-hoc Tukey pairwise comparisons to examine significant results.

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Highlights

- DG and CA3 structure is consistent with pattern separation and pattern completion
- CA3 backprojections are potentially important in pattern separation and completion
- Granule cell mossy fiber variance is also potentially important
- Hilar ectopic granule cells exemplify dominant granule cells
- Dominant granule cells may emerge in due to hormonal changes or disease

Figure 1.

Modeling the DG-CA3 network. A1. The structure of the rodent DG is shown. There are three divisions of the molecular layer (MOL; outer, middle and inner), a granule cell layer (GCL) and hilus. The dotted line distinguishes the hilus from area CA3. In CA3 there are several layers: stratum oriens (SO), stratum pyramidal (SP), stratum lucidum (SL) where the mossy fiber pathway is located, stratum radiatum (SR) where the recurrent collaterals of pyramidal cells terminate, and stratum lacunosum-moleculare (SLM) where the entorhinal cortical projection (perforant path) innervates CA3 pyramidal cell distal dendrites. A2. Simplified schematic of some major pathways and cell types in the DG-CA3 model are shown. PP= perforant path. IN=interneuron. There are two types of IN shown in the DG, a perisomatic-targeting cell exemplified by the 'basket' cell with a pyramidal morphology (triangle) and a dendritic-targeting cell represented by the HIPP cell (oval; HIPP= hilar cell with an axon targeting the layer containing the perforant path terminals). INs are also located in CA3 (oval). Note that the mossy fibers have both giant boutons as well as filamentous extensions that make synapses, primarily onto IN. MC=mossy cell. PYR= pyramidal cell. GC=granule cell. From (Myers et al., 2013). B. The DG-CA3 network model. Abbreviations as in part A. β_{HIPP} , β_{MC} and β_{IN} are constants governing connection strengths in the model. For additional details, see (Myers & Scharfman, 2011; Myers et al., 2013).

Figure 2.

Characteristics of the DG-CA3 network consistent with pattern separation and completion.

A. The estimates of neuronal numbers for entorhinal cortex layer II neurons (the cells of origin of the perforant path projection, PP), DG GCs and CA3 pyramidal cells suggest a sparsification from the entorhinal cortex to the DG and CA3. B. Intrinsic properties of GCs make them unlikely to discharge repetitively for a very long time. An example is shown: a maintained depolarization to a GC (rectangular step) leads to a train of 4 action potentials with increasing interspike intervals. From (Scharfman et al., 2000). C1. The 'backprojection' of CA3 pyramidal cells (red) targets interneurons (IN) that innervate GCs (Scharfman, 2007a). The circuit that results is PP → GC → pyramidal cell → IN → GC and leads to GC inhibition. C2. The backprojection also innervates hilar mossy cells (MC) that

innervate local INs to silence local GCs: PP → GC → pyramidal cell → MC → IN → GC (Scharfman 1994a,b; 1995). C3. Even if a given pyramidal cell does not project back to the DG, it may do so indirectly by recurrent collaterals to other pyramidal cell. C4. A schematic of a GC firing in response to the perforant path input (green arrow) or being silenced (red x) by inhibitory pathways as illustrated in C1 (A), C2 (B) or C3 (C). The result is inhibition of persistent GC firing. The backprojection shown in C1-C3 can potentially inhibit firing of GCs that were recently activated, and do so at different latencies. This would occur in the same lamella as the one where the GC was originally activated, because the circuitry in C1-C3 is primarily lamellar (Amaral & Witter, 1989). The outcome would be silencing of GCs in the same local area as those GCs that were recently activated by the perforant path.

Figure 3.

Hilar ectopic GCs (hEGCs). A1. A calbindin-stained section from a control rat shows stained GCs in the granule cell layer (GCL), their dendrites and axons. Calibration (different sizes in A, B and C) is 100 μ m. A2. A calbindin-stained section from a rat that was epileptic shows numerous calbindin-stained cells in the hilus (box) which is enlarged in A3. Arrows point to hEGCs. From (Scharfman et al., 2000). A4 A schematic illustrates the potential dominance of hEGCs (red) over normal GCs in the granule cell layer (grey) in the epileptic DG-CA3 network. B1-B2. Examples of hEGCs from epileptic rats. The hEGC was filled using an intracellular recording electrode which was also used to confirm the intrinsic electrophysiological properties were similar to GCs in the granule cell layer. B1 was previously shown in (Scharfman et al., 2000). C1-C4. A hEGC in a *BAX*^{-/-} mouse showing the drawing (C1), filled cell (C2), location (C3) and mossy fiber axon (C4). From (Myers et al., 2013).

Figure 4.

Effect of hEGCs in a computational model of DG-CA3. A. Three models were compared, a “Standard,” “New,” and “Intermediate” model. The Standard model was similar to that illustrated in Figure 1B and included entorhinal cortex (perforant path) inputs that projected directly to a CA3 network as well as indirectly via a DG network in which all GCs were “mature” and placed in the GC layer. The Intermediate model included a small proportion (5%) of “immature” GCs, located as usual in the granule cell layer, but slightly more excitable than normal “mature” GCs. The New model also included 5% immature GCs, but these were placed in the hilus, simulating hEGCs. B. To test pattern separation, pairs of entorhinal input patterns were presented, and correlation was computed between the output patterns generated in the DG or CA3 to the two input patterns. In the Standard model, average correlation was low in the DG, indicating successful pattern separation. Average correlation was also low in CA3 although the average correlation increased slowly as the number of trained input patterns increased. Results were similar in the Intermediate model. However, the average correlation was much higher in both the DG and CA3 of the New model, indicating decreased pattern separation when hEGCs were present. C. As a measure of pattern completion, the models were allowed to store a set of entorhinal input patterns and then tested with “partial” versions of the stored patterns in which various proportions of active elements were silenced (% degradation). When the number of stored patterns was low (C1), both the Standard and Intermediate models could usually retrieve the correct stored pattern even when degradation was high (e.g. up to 90% degradation), but the New model was severely impaired compared to the other models even when % degradation was low. When the number of stored patterns was high (C2), all models were impaired but the New model was most severely deficient. Together, these results indicate that presence of a small population of modestly hyperexcitable (immature) GCs in the granule cell layer is not sufficient to disrupt model behavior, but presence of a small population of dominant hEGCs

disrupts both pattern separation and pattern completion. A and C were adapted from (Myers et al., 2013). B was based on modeling results presented previously (Myers et al., 2013).

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Figure 5.

Effects of hEGCs on GC firing in the Standard, Intermediate and New models (from Figure 4A). The percent of GCs that have suprathreshold activity (firing) are shown for different GC subtypes in the three computational models. In the Standard model, a small percentage (about 2%) of mature GCs fire in response to input from the entorhinal cortex along the perforant path. In the Intermediate model, a similar percentage of mature and immature GCs fire in response to perforant path input. But in the New model, the hEGCs are dominant, reflected in much higher firing rate of hEGCs relative to mature GCs in the granule cell layer, and a reduced rate of mature GCs compared to the Standard model. Thus, in the New model, the dominant hEGCs are not only highly active, but suppress activity in other non-dominant GCs. This leads to reduced variance in the GC input (mossy fibers) to CA3, which in turn produces the impaired pattern separation and completion seen in the New model (Figure 4B,C). Adapted from Figure 8A in (Myers et al., 2013).

Figure 6.

The “dominant GC” hypothesis. A. Normally, a given entorhinal cortex (perforant path) input pattern activates a small number of GCs (red circles) which project via mossy fibers (arrows) to a group of pyramidal cells (red triangles); recurrent collaterals between co-active pyramidal cells can be strengthened, forming a cell assembly encoding that pattern. A different entorhinal input pattern activates a different subset of GCs and pyramidal cells (blue), which form a new cell assembly in CA3. B. A small group of “dominant GCs” (red) respond to many entorhinal input patterns and repeatedly target the same pyramidal cells (red), which become linked into a strong cell assembly that recruits additional pyramidal cells (blue). The outcome is impaired pattern separation and also impaired pattern completion (as shown in Figure 4B,C), because presentation of any entorhinal inputs will tend to evoke activity in the same subset of CA3 pyramidal cells.

Figure 7.

Three DG-CA3 network models with different degrees of dominant GCs. As in Figure 5, the percent of GCs that have suprathreshold activity (firing) are shown for different GC subtypes. As in prior figures, presentation of entorhinal cortex input patterns in the Standard model produces sparse firing in the GCs located in the granule cell layer (black bar).

However, when a small proportion (5%) of these GCs are made weakly dominant (Weakly-dominant model), by reducing the firing threshold from +0.75 to +0.05, many more of these dominant GCs fire in response to entorhinal input (light red); there is no change in firing among the remaining GCs (non-dominant, bright red). When the same small proportion of GCs (5%) are made strongly dominant (Strongly-dominant model) by reducing their firing threshold to 0.0, all of the dominant GCs (light red) fire in response to any entorhinal input. The non-dominant GCs remain unaffected (bright red). These findings are a contrast to Figure 5, where the presence of hEGCs (dominant GCs that are located in the hilus) produced a reduction in firing of GCs in the granule cell layer.

Figure 8.

Pattern separation and pattern completion in the Standard, Weakly-dominant, and Strongly-dominant models (described in Figure 7). The presence of a small population (5%) of weakly-dominant GCs impaired pattern separation, indicated as increased correlation among the responses to stored patterns in both the DG (A1) and CA3 (A2). There also was impaired pattern completion (B1-B2), indicated as reduced ability to successfully retrieve stored patterns when partial (degraded) versions of those patterns were presented as input. The presence of strongly-dominant GCs severely degraded both pattern separation and pattern completion.

Figure 9.

Increased mossy fiber variance with reduced testosterone levels in male rats. A.

Gonadectomy of adult male rats led to structural plasticity of mossy fibers, reflected by mossy fiber sprouting into stratum oriens of CA3 (arrows). Surgery was conducted in young adult rats and comparisons were made between gonadectomized animals and age-matched animals subjected to anesthesia and surgical opening of the abdomen, but no gonadectomy. The mossy fibers are stained by one of the peptides normally present in mossy fibers, dynorphin. Calibration in A1, 500 μm ; calibration in A2, 100 μm . Abbreviations as for previous figures. From (Skucas et al., 2013). B. Current source density analysis showed that in normal male rats, mossy fiber stimulation in hippocampal slices evoked a field potential with a sink in stratum lucidum (red arrow) followed by a later sink in stratum radiatum (red arrowhead). This pattern of activation is consistent with mossy fiber excitation of proximal pyramidal cell dendrites followed by recurrent collateral excitation of more distal dendrites. From (Skucas et al., 2013). On the right is a CSD for a gonadectomized male rat showing that the normally focal sink in stratum lucidum has lost its afferent specificity, indicating greater mossy fiber variance. From (Skucas et al., 2013).