

How Heterogeneous Place Cell Responding Arises From Homogeneous Grids—A Contextual Gating Hypothesis

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ABSTRACT: How entorhinal grids generate hippocampal place fields remains unknown. The simplest hypothesis—that grids of different scales are added together—cannot explain a number of place field phenomena, such as (1) Summed grids form a repeating, dispersed activation pattern whereas place fields are focal and nonrepeating; (2) Grid cells are active in all environments but place cells only in some, and (3) Partial environmental changes cause either heterogeneous (“partial”) remapping in place cells whereas they result in all-or-nothing “realignment” remapping in grid cells. We propose that this dissociation between grid cell and place cell behavior arises in the entorhinal-dentate projection. By our view, the grid-cell/place-cell projection is modulated by context, both organizationally and activationally. Organizationally, we propose that when the animal first enters a new environment, the relatively homogeneous input from the grid cells becomes spatially clustered by Hebbian processes in the dendritic tree so that inputs active in the same context and having overlapping fields come to terminate on the same sub-branches of the tree. Activationally, when the animal re-enters the now-familiar environment, active contextual inputs select (by virtue of their clustered terminations) which parts of the dendritic tree, and therefore which grid cells, drive the granule cell. Assuming this pattern of projections, our model successfully produces focal hippocampal place fields that remap appropriately to contextual changes. © 2008 Wiley-Liss, Inc.

KEY WORDS: place cells; grid cells; dentate gyrus; space; context

INTRODUCTION

The hippocampal place cells (Fig. 1) were first observed by O’Keefe and Dostrovsky (1971), and their discovery led to O’Keefe and Nadel’s renowned hypothesis that these neurons collectively act to construct a representation of extra-personal space called a “cognitive map” (O’Keefe and Nadel, 1978). The critical properties leading to the cognitive map hypothesis are that the places where the cells fire (the place fields) are spatially localized, tend to be constant in a given environment, are very stable over several or many days, and occur independently of any particular focal environmental stimulus, seemingly arising from a more holistic processing

of many stimuli. A longstanding and important question concerning the place cells is how their firing fields could be generated from incoming inputs.

The answer to this question received a great boost with the recent, surprising discovery of grid cells (Fig. 1) in the dorso-medial entorhinal cortex (Hafting et al., 2005), one synapse upstream from the place cells (Moser and Moser, 2008). Grid cells have several similar properties to place cells: they also produce firing fields with locations characteristic for a particular environment, are stable across days and are independent of focal stimuli. They have additional unique features: most notably that their firing fields are multiple, recur at regular intervals across the surface of the environment, occur (as far as is known) in every environment (unlike place cells which only tend to be active in some environments) and are oriented, in as much as their grid-like rows of peaks preserve the same orientation from one recording session to the next. The facts that grid cells from a particular region seem to have the same orientation (Hafting et al., 2005), and maintain the same spatial phase relationship when changes occur to the environment (Fyhn et al., 2007) have suggested that the activity of the neurons is interlinked, perhaps by attractor network processes (McNaughton et al., 2006).

Now that grid cells are known about, the generation of place cell activity from entorhinal inputs should be easier to elucidate, and indeed several groups have produced models of how this might occur. In their original grid cell report, Hafting et al. suggested that hippocampus might function to associate the generalized grids with specific landmark information, but did not speculate on the transformation between grid cell and place cell activity. The first transformational model was put forward by O’Keefe and Burgess (2005), who proposed that grid cells with peak firing at a given location could be connected to place cells with place fields centered at that location. So long as the grids vary in both scale (i.e., interpeak distance) and offset (peak location), their combined activity would produce place cell activity only at the place where the summed inputs from the grids exceeded a given threshold. Rolls et al. (2006) showed that such a mapping could be achieved by a competitive learning network, and Solstad et al. characterized the phenomenology of the place fields that would theoretically result from the summed activity of grid cells

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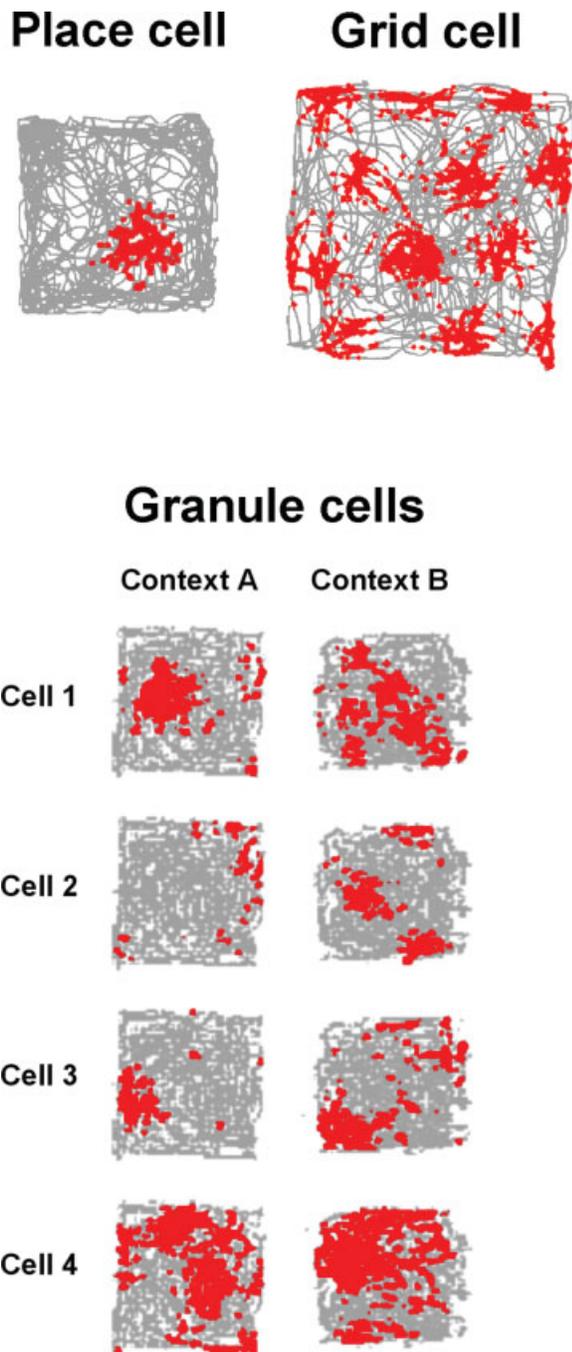


FIGURE 1. Typical firing patterns of a place cell and grid cell (top) and four dentate granule cells in two contexts (bottom). In each case the rat, whose path is shown in gray, was foraging in a square environment while the cells were being recorded. Gray shows the locations of the rat and red marks the places where the cells fired. Note that the place cell fires in a single location in the environment whereas the grid cell repeats its activity at regular intervals across it. The granule cells show an intermediate pattern with irregular, multi-peaked fields. Note the change in the firing pattern in response to a change in context. Top figures adapted from (Jeffery and Burgess, 2006) and bottom from (Leutgeb et al., 2007). [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

of different scales and offsets, and random orientations (Solstad et al., 2006). All these models have in common the assumption that grids of different scales summate, perhaps via weighted connections, to produce place fields.

Although summation models are intuitively appealing, in their simplest form they fail to account for a number of features of place field phenomenology. Simple summation of grids produces activation patterns that are regular and spread across the environment, whereas place fields are focal and often irregular. Although this regularity can be broken by varying the orientation of the grids, there is currently scant evidence for varied orientations of grids occurring simultaneously in a given animal.

A final problem for the simple summation hypothesis is that grid cells and place cells frequently apparently dissociate their responses to some kinds of environmental change. These responses are collectively known as “remapping,” and they occur in a variety of ways. When an animal is placed in a new environment, place cells alter their responding by changing their firing location or their firing rate. Although there are some differences in responding between CA3 and CA1 (Guzowski et al., 2004), typically only about 50% of place cells active in one environment will also be active in a second, and their activity in that second environment cannot be predicted from that in the first, suggesting that a complete new representation (or “map”) has been formed. When all observed cells alter their responses together in response to an environmental change then the phenomenon is known as global remapping, and when only some cells respond then they are said to have undergone partial remapping.

Can place cell remapping be understood in terms of what happens to the grid cells? Indeed, global, “complete” remapping may have a relatively straightforward explanation, because when

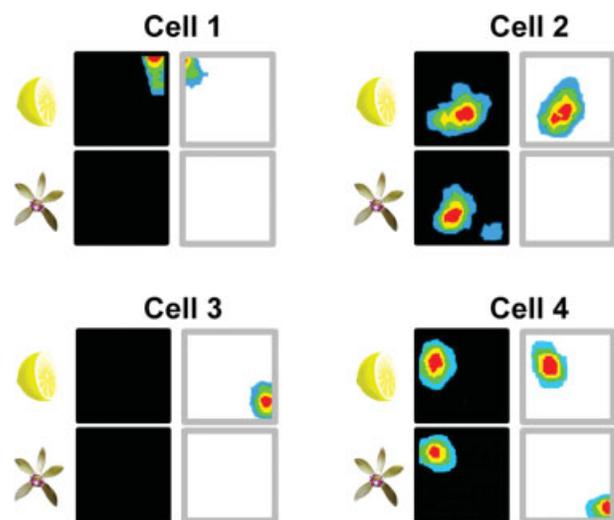


FIGURE 2. Partial remapping of place cells, where independent change of color and odor causes different place cells to respond differently. Figure adapted from (Anderson and Jeffery, 2003). [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

complete changes are made to an environment, inducing global remapping in place cells, grid cells both shift and rotate their grids (Fyhn et al., 2007). Thus, a complete change in the grid cell activity pattern (i.e., one affecting the whole population at once) corresponds to a complete change in place cell responding.

Incomplete remapping phenomena such as partial remapping (Fig. 2) are harder to explain in grid cell terms, as there is currently no evidence that grid cells can remap partially (i.e., with some remapping and some not). Thus, in the present article, we present an alternative explanation for partial remapping, which is that the grid cell/place cell mapping is gated by the contextual cues.

Our proposal, which is outlined in the remainder of this article, is that the grid-cell/place-cell mapping is regulated by a convergent set of nongrid-cell inputs, arising from lateral entorhinal cortex and carrying what will be referred to as “contextual” information, which functions to select which of the incoming grid cell inputs will drive a given place cell in a particular environment (see also Redish, 1999; Hargreaves et al., 2005; Lipton and Eichenbaum, 2008). We propose that the first step of this interaction takes place in the dentate gyrus, where neurons show firing patterns intermediate between grid and place cells (Fig. 1). We formulate a model of how this might occur and show that it can account for both the focal and irregular nature of place fields and also for contextually induced place field remapping.

Outline of the Model

The basis of our model is that convergent contextual inputs act to regulate the grid-cell/granule-cell connection in the dentate gyrus. A plausible source for this contextual information is the lateral EC, which evidence suggests carries nonspatial information to the same areas as the grid cells (Hargreaves et al., 2005). Medial and lateral EC project to the dentate gyrus via medial and lateral perforant paths respectively, and these pathways have termination zones on the granule cell dendrites that are distinct both anatomically (Hjorth-Simonsen, 1972) and physiologically (McNaughton and Barnes, 1977). Our model thus focuses on this region and proposes that the conversion from uniform and regular grids to punctate and irregular place fields occurs by means of cooperative interactions in this laminated dendritic tree.

The stratified layout of the connections of the dentate gyrus is shown in Figure 3. Entorhinal fibers originating from Layer II stellate cells make contact with the distal dendrites, and commissural/associational fibers contact the proximal dendrites (Forster et al., 2006). In addition, neurons from the deeper entorhinal Layers (IV–VI) make contact with proximal parts of the same dendritic trees in the dentate gyrus (Deller et al., 1996). This stratification of excitatory inputs is mirrored by a similar stratification of local inhibitory interneurons, with morphologically different interneurons associated with the molecular and commissural/associational perforant path termination fields (Halasy and Somogyi, 1993). This pattern of spatially differentiated termination suggests a role for dendritic location of inputs in controlling activity. Previous physiological studies

have shown that the middle molecular layer of the dentate gyrus shows selective cholinergic suppression (Kahle and Cotman, 1989), and it has been suggested that a function of this differential modulation might be to allow associative processes among inputs from medial entorhinal cortex to be suppressed, while self-organization takes place among inputs from lateral EC (Hasselmo and Schnell, 1994).

We present here a slightly different (or perhaps complementary) proposal, which is that the contextual inputs in the distal branches interact cooperatively with the spatial inputs in the middle branches, perhaps reinforced by additional feedback inputs onto the most proximal parts of the dendritic tree. These contextual inputs regulate the grid-cell-dentate projection in two ways, which can be characterized as organizational and activational. Organizational regulation refers to the way in which the inputs caused connections to be established when the animal first encountered a particular context. The term “activational” refers to the external imposition of activation onto the inputs—*in vivo* we would, of course, expect this to occur as the animal explores particular environments, but in our simulation it is imposed on the system by an arbitrary selection of the inputs onto our simulated granule cells. The different inputs thus correspond to different contexts.

Our model is not a detailed, mechanistic simulation of grid cell/dentate interactions, but it aims to reproduce the phenomenology of dentate granule cell firing fields and CA3 place fields by assuming particular constraints on the mapping between grid and granule cells. Data published on dentate place fields are limited, but we have used, as a guide, the data set presented by Leutgeb et al. (2007), in which granule cells fire multi-peaked and irregular place fields (an average of 1.7 fields per environment, according to calculations performed by A. Treves, pers. comm.). We begin by presuming that a dentate granule cell initially receives plentiful and random inputs from large numbers of grid cells of varying scales. This would result in the cell's being active in all environments (as grid cells are thought to be) and also firing in all regions of the environment. We thus propose (albeit do not simulate) that over time, the inputs become clustered by Hebbian cooperativity with simultaneously active contextual inputs, so that grid cells having overlapping firing fields in particular regions of the environment will tend to converge onto a particular region of a granule cell's dendritic arbor (Fig. 3C). We show that such a clustering mechanism can explain how punctate and irregular firing fields can be produced from inputs that are, in themselves, dispersed and regular.

Our next organizational proposal is that the contextual inputs themselves become clustered, again by a Hebbian mechanism, so that those inputs active in a given context will themselves come to terminate on a given part of the dendritic tree. Thus, coactive spatial and contextual inputs have, by a bootstrapping mechanism, reinforced each other via interactions within the dendritic tree, so that contextual inputs active in a given context will preferentially innervate one part of the dendritic tree, and spatial inputs coactive in one region of the environment (i.e., with overlapping offsets) will also innervate part of the dendritic tree.

Finally, we propose the activational effect of context—having established the above wiring patterns, when an animal enters a particular environment the inputs active in a given context will act cooperatively with the spatial inputs terminating on that same part of the dendritic tree, so that only those particular inputs will drive the granule cell. We model the outcome of activation by contextual cues and show that this could generate context-specific patterns of activity in the dentate gyrus, which in turn translate to context-specific patterns of activity in CA3 that resemble those occurring in real animals.

METHODS

All simulations were conducted in Matlab (The Mathworks, Natick, MA). Our simulation is constructed in five stages, listed below and detailed thereafter:

1. Generation of a set of “basis grids,” serving as simulated grid cell inputs, all having the same orientation but varying in two parameters, called interpeak distance (also called grid scale, or wavelength) and offset, which is the location of a fixed grid cell peak shifted from the center by a specified amount, around which the remainder of the grid is organized.
2. Clustering of the entorhinal inputs onto dentate granule cells so that cells with overlapping fields in a particular part of the environment will tend to coterminate on the dendritic tree. This is the first organizational effect of the contextual inputs, and is captured by the “offset clusters” described below.
3. Clustering of contextual inputs onto these same cells (the second organizational effect) and specification of the activation rules that drive each granule cell (the activational effect).
4. Clustering of the dentate inputs to CA3 cells, and specification of the activation rules driving each CA3 cell.
5. Induction of remapping by altering contextual inputs.

The results of the above manipulations were quantified by assessing firing field size, number of subfields, spatial information, and spatial coherence. Firing field size was assessed by summing the number of bins that contained any firing above 0 Hz. The number of subfields was calculated by finding regions of pixels that had contiguous firing. A subfield was considered to be a contiguous set of pixels, each of which had activity both in itself and in any of the nearest eight surrounding pixels. Spatial information was assessed by the method outlined by Skaggs et al. (1993), and provides a measure of how much information the cell is providing the rat about its current location. Spatial coherence was assessed by the method established by Muller and Kubie (Muller et al., 1987), which provides an assessment of the orderliness of each cell’s firing field. Correlations between firing rate maps were calculated by converting each of the to-be-correlated firing maps to an ordered list of pixels, removing the pixels in which there was no activity in either map (to avoid inflating the correlation with large numbers of empty pixels), performing a Pearson’s correlation on the remaining values and then z -transforming these scores.

Generation of Basis Grids

Our simulation took place in an imaginary 1-m square environment from which it was assumed all positions were equally sampled, and the first step was to generate the “basis grids” from which the inputs to each model granule cell would be selected.

The parameters that describe a grid are orientation, grid scale, and offset (Fig. 4A), and so our model grid cells were specified along each of these dimensions. Orientation refers to the angle made by a line of grid peaks, and available evidence suggests that the orientation in a given environment is constant across a population of simultaneously active grid cells (Hafting et al., 2005), so we did not vary orientation in the model. Grid scale, or wavelength, is the distance between the peaks of grid cell activity, and it varies from around 30 cm in the most dorsal regions of EC to very large—up to 3 m—ventrally (Brun et al., 2008). Cells from a wide range of dorso-ventral regions project to a given region of the dentate gyrus (Witter, 1993), so we chose the inputs to each granule cell from a range of 12 grid scales, increasing linearly from 30 cm up to 206 cm. The lowest wavelength value was chosen based on current data; the upper limit was extrapolated from current data together with the known anatomy of the medial EC (McNaughton et al., 2006). Offset refers to the position of peaks within an environment. In our model, we chose the center of the box as a reference, and specified offset as being a fixed peak shifted relative to this center to anywhere within the environment (Fig. 4A), against which all other peaks were referenced.

To produce the simulated grid cell activations, we used the method of Solstad et al. (Solstad et al., 2006). The grids were assembled by adding three two-dimensional cosine functions (Fig. 4A) with gratings oriented $\pi/3$ apart in the plane, that is,

$$\psi(r) = \frac{\cos(k_1 r) + \cos(k_2 r) + \cos(k_3 r)}{3}$$

where $r = [x, y]$, and

$$k_1 = \frac{k}{\sqrt{2}} \cdot \left[\cos\left(\theta + \frac{\pi}{12}\right) + \sin\left(\theta + \frac{\pi}{12}\right), \cos\left(\theta + \frac{\pi}{12}\right) - \sin\left(\theta + \frac{\pi}{12}\right) \right],$$

$$k_2 = \frac{k}{\sqrt{2}} \cdot \left[\cos\left(\theta + \frac{5\pi}{12}\right) + \sin\left(\theta + \frac{5\pi}{12}\right), \cos\left(\theta + \frac{5\pi}{12}\right) - \sin\left(\theta + \frac{5\pi}{12}\right) \right],$$

$$k_3 = \frac{k}{\sqrt{2}} \cdot \left[\cos\left(\theta + \frac{3\pi}{4}\right) + \sin\left(\theta + \frac{3\pi}{4}\right), \cos\left(\theta + \frac{3\pi}{4}\right) - \sin\left(\theta + \frac{3\pi}{4}\right) \right],$$

so that $|k_1| = |k_2| = |k_3| = k$.

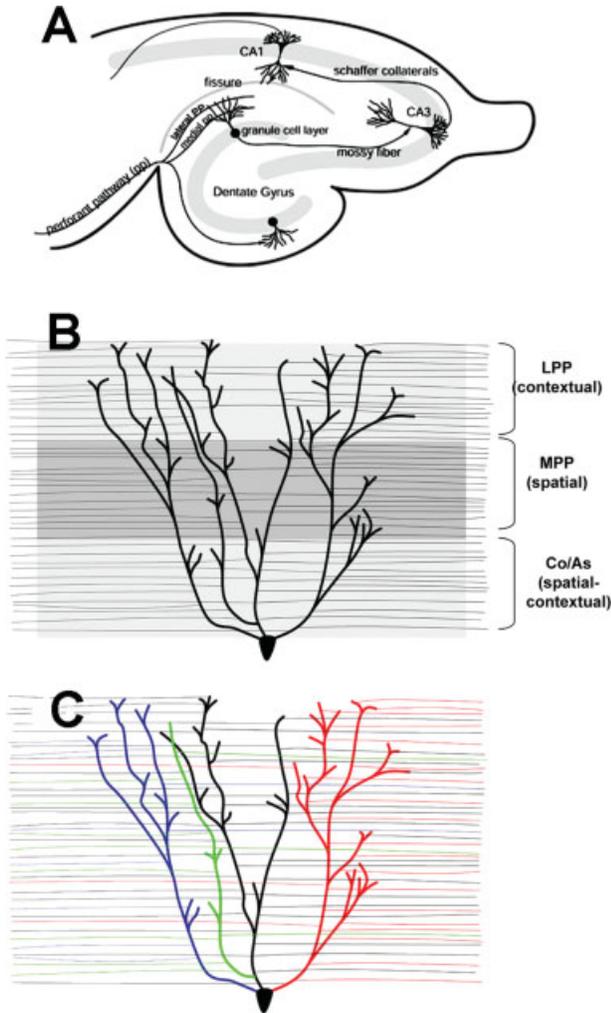


FIGURE 3. (A) Diagram of the hippocampal circuitry showing the laminated termination zones of lateral vs. medial perforant path inputs onto dentate gyrus [Adapted from (Dimoka et al., 2006)] (B) Diagram showing the hypothetical information content of the various inputs to the granule cell dendritic tree, with contextual inputs arriving distally via the lateral perforant path (LPP), spatial inputs arriving in the middle third via the medial perforant path (MPP), and preprocessed inputs arriving via the commissural-associational projection (Co/As) from contralateral hippocampus. Note that the granule cell only has a few primary dendritic segments—we suppose that these loosely correspond to offset clusters. (C) Clustering of coactive inputs results in separation of inputs according to where they terminate on the granule cell dendritic tree. Four hypothetical contexts are shown in different colors. The dendrites are shown in corresponding colors, indicating that different parts of the tree come to be active in different contexts. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

To obtain a grid function with a peak at any arbitrary spatial location r is replaced with $r - r_0$, that is,

$$\Psi_w(r) = \Psi(r - r_0),$$

where w denotes the three parameters that describe the grids; that is, $w = (\lambda, \theta, r_0)$, where the three parameters are spacing, orientation, and phase, respectively (see below for details).

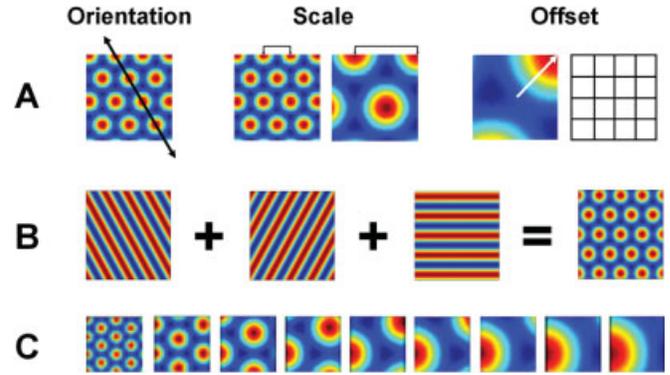


FIGURE 4. The set of grids used to generate the granule cell place fields. (A) The relevant parameters specifying a grid cell grid are orientation (angle formed by the rows of peaks), scale (inter-peak distance, shown here for a small and medium-scale grid), and offset (deviation of the grid from central alignment, shown here for a very large-scale grid). The dotted grid on the far right shows the 16 offset regions used to cluster the inputs in the present model. (B) Summation of three sinusoidal gratings at three different orientations to produce a hexagonal pattern representing activation of a given grid cell. (C) An example set of “basis grids” spanning all the offsets and all the grid scales used here. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

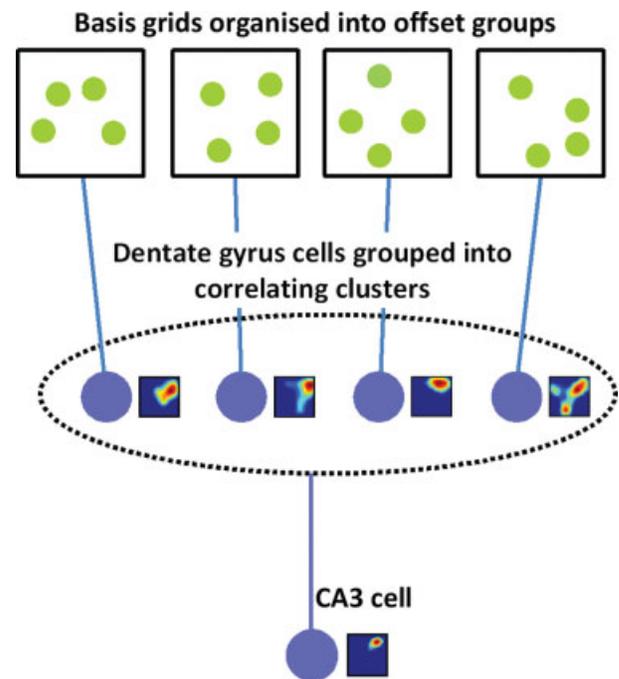


FIGURE 5. Diagram showing the way in which grid cells with common offsets (shown by the green circles) projected to granule cells, which thus tend to have a dominant activity peak in a small number of regions of the environment. In turn, granule cells with overlying fields (reflected in high correlation values) project to common CA3 cells. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

The output range of the grid function $\psi_w(r)$ is $-1/2$ to 1 . The firing rates of the individual grid cells was adjusted to lie between 0 and g_w^{\max} where g_w^{\max} denotes the maximum firing rate (this was set to a value of 10 Hz). Therefore, grid cell functions are defined as

$$g_w(x, y) = g_w^{\max} \frac{2}{3} \left(\psi_w(r) + \frac{1}{2} \right)$$

The cosine functions have an angular difference of 60° from one another and when summed produce the appropriate grid.

Clustering of Entorhinal Inputs Onto Dentate Granule Cells

The resulting set of basis grids, spanning the whole range of offsets and grid scales (wavelengths), were used to form the origin of projections to the simulated granule cells. The time window for summation of excitatory postsynaptic potentials in dentate dendrites is extremely short—around 10 ms (Schmidt-Hieber et al., 2007)—meaning that only near-simultaneous EPSPs are likely to summate enough to depolarize the cell. For this reason, and also because it generated more realistic-looking granule cell fields (see Results), in our model we assume that simultaneously active grid cells (i.e., those with overlapping fields) will preferentially drive a given granule cell. We thus specify a parameter called “offset” (see Fig. 4A) that identifies a fixed peak for every grid cell—groups of cells with offsets falling within the same subregion of the environment ($1/16$ th of the total area) are henceforth referred to as “offset clusters,” and each granule cell will receive inputs from only a few offset clusters (this procedure is similar to that of Solstad et al., 2006). This was achieved by clustering the grid inputs such that each granule cell was connected to N clusters (N varying from 1 to 16) of grid cells, where each cluster had the same phase or offset from the center of the environment. The effects of varying the number of offset-clustered inputs is one of the factors explicitly assessed in the model.

It should be noted that for simplicity, and to avoid the generation of a large number of empty firing rate maps, we did not attempt to introduce sparsity into the projection, though this would be easy to do by just assuming that most granule cells receive activation of too few offset clusters to even fire at all in most environments. Thus in our model all the granule cells are always active somewhere in a given environment, whereas in reality, very few are (Jung and McNaughton, 1993; Chawla et al., 2005; Leutgeb et al., 2007).

Clustering of Contextual Inputs Onto These Same Cells, and Specification of the Activation Rules That Drive Each Granule Cell

As mentioned earlier, as well as context-modulated organization of the spatial inputs onto the granule cells, we also propose the converse: organization of the contextual inputs so that these too are clustered. We assume a mutually interactive, bootstrapping process whereby inhomogeneities in the contextual

inputs to the dendritic tree facilitate clustering of the spatial inputs, and these in turn cause clustering of the contextual inputs by the same process. The end result is that grid cells of a particular offset tendency will converge on the same subsection of the dendritic tree as contextual inputs active in a given context. Only when all the cells are coactive (i.e., the animal is in a particular place in a particular context) will depolarization from this branch of the dendritic tree be able to spread to the soma and help drive the cell.

Clustering of the Dentate Inputs to CA3 Cells, and Specification of the Activation Rules Driving Each CA3 Cell

We now take a step further, and suggest a means by which the multi-peaked fields in dentate gyrus might be transformed into the generally singular fields found in CA3. The model presumes that again, the projections from granule cells to CA3 cells are clustered such that granule cells with overlapping fields will preferentially project to a given CA3 target (Fig. 5). Spatial clustering was introduced into the dentate-CA3 mapping by finding granule cells whose fields were highly correlated with one another; each CA3 cell received an input from at least three such well-correlated cells. Therefore, the inputs that a single CA3 cell received had to have similar but nonidentical receptive field patterns.

Each dentate gyrus granule cell received inputs from a number of grid cells that was varied systematically. The sum of the inputs a given granule cell received was normalized by the number of incoming inputs. All dentate granule cells were also subject to a spatially nonspecific global inhibition, that is,

$$DG(x, y) = \sum_1^n \frac{g_w(x, y)}{n} - C_{\text{inh}}$$

where n represents the number of inputs a given cell receives and C_{inh} , the inhibitory input.

As with the dentate granule cell population, the sum of the inputs a CA3 cell received was normalized by the number of incoming inputs and subject to global inhibition, that is,

$$C(x, y) = \sum_1^n \frac{DG(x, y)}{n} - C_{\text{inh}}$$

The clustering of inputs from granule cells to CA3 was achieved as follows: dentate activation maps were generated, and then each cell in the baseline map was then correlated on a pixel-by-pixel basis with every other cell in that map, and a list generated of other cells whose firing correlated to a level of 0.5 or higher. The pair of cells with the highest correlation (i.e., the most coactive pair) was then mapped to an imaginary CA3 cell on an exclusive basis so that once mapped to one CA3 cell, a cell could not map to another (although more than one dentate cell could map to the same CA3 cell). If one of the cells in a correlating pair had already been mapped to a CA3 cell, its partner was also mapped to that same cell. The

correlation procedure was then repeated for each successive dentate cell pair, in descending order of correlation strength, until the whole population of dentate cells was mapped, in clusters, onto a smaller number of CA3 cells.

Induction of Remapping by Altering Contextual Inputs

Finally, remapping was produced by altering the contextual inputs to the granule cells. This was simulated by switching whole offset clusters on and off, as if the animal had been moved to a new environment, in which different contextual inputs were active. The resulting changes in activation were then propagated down to the CA3 layer.

Because we assume coactivity-induced clustering of the granule cell inputs onto CA3 cells, it was necessary to include the inputs to the cells for both the baseline and the remapped conditions, since the same population of cells is activated by the two “contexts” (albeit expressing different firing patterns), and yet there is only one wiring configuration for the network. Thus, we clustered the inputs from dentate gyrus to CA3 by using both maps, with the result that if a connection were strengthened in environment A, that strong connection would now contribute to activation in environment B.

We simulated these plastic processes by generating both of the maps, correlating each granule cell with each of the others within each map, and then listing the combined cell-pairs in descending order of correlation as before. Then the clustering procedure was conducted as above, with each cell pair being allocated to a new CA3 cell unless one of the cells had already been assigned, in which case its pair was also added to the input set for that cell. Because this was done using both maps from both contexts, clustering of the dentate inputs to CA3 now took into account correlated activity in either of the two conditions.

RESULTS

Summation of the Basis Grids to Produce Hippocampal Place Fields

The first step was to sum subsets of the basis grids to produce activation of the model granule cells. Our aim was to try and produce granule cell place fields that resemble those seen experimentally: data on this issue are limited, and we chose to use the data presented in the recent article by Leutgeb et al. (2007) (Fig. 1). In this article, dentate place fields typically have between one and four subfields (averaging 1.7, as mentioned above).

Because of the regularity of grid cell grids, summation of even a small number of grid cells of different spatial scales tends to produce a uniform activation pattern across the entire environment, which contrasts with the relatively punctate and irregular nature of real dentate firing fields. One way to make

the fields look realistic would be to introduce heterogeneity into the grid peaks, so that for a grid, some peaks would be stronger than others, as Rolls et al. have done (Rolls et al., 2006). However, this requires considerable spatial input into the first layer of the model, which is undesirable since a spatial computation is supposed to be its output. An alternative, which we chose, is to follow Solstad et al. (2006) in presuming that there is an inhomogeneity in the selection of grids that project to a given granule cell, such that the grids that project to a given cell in any given environment will tend to have firing fields that overlap in one part of the environment, producing a peak of activation at that point. The rationale for this derives from the assumption that on a dentate dendritic tree, neighboring inputs will tend to mutually potentiate if they are coactive. This procedure still requires that spatial information form a component of the inputs to the cell, in as much as the grids need to be fixed to the environment by spatial cues in order for the point of overlap to be constant from trial to trial, but this only need be at one point per cell (perhaps corresponding to a single environmental feature).

We modeled this inhomogeneity by spatially clustering the inputs to the granule cell as described in the Methods. We divided the square environment into 16 equal “offset regions” and then selected the inputs such that they were chosen from only N of the available 16 regions, where N was varied from 1 to 16. A group of inputs whose offsets all fell within a given one of these 16 offset regions is called an offset cluster. The rationale for offset clusters is that during establishment of a representation, grid cells having a particular offset will tend to have neighboring termination zones in the dendritic tree, due to the postulated Hebbian process mentioned above.

The effects on granule cell activation of varying the number of offset clusters driving it were assessed (Fig. 6). With too few clusters, the fields became singular and overly regular, and with too many offsets they became dispersed and covered the whole of the environment.

Interestingly, the number of subfields was not a monotonic function of the number of clusters the inputs were grouped into (Fig. 6B). Although it is true that increasing the number of offset clusters will necessarily increase the “lumpiness” of the firing distribution, this effect was counteracted by the concomitant increase in field size, so that the number of subfields peaked at around 3–4 clusters and then declined again. The firing fields produced by 3–4 clusters were those that most resembled real data, and were relatively insensitive to changes in input number. Thus, from this point onward we chose four offset clusters as the structure for the grid cell-dentate projection and assumed 96 inputs per offset cluster, of randomly selected wavelength, to form the network structure for the subsequent analyses.

The effects of varying the number of inputs per offset cluster was assessed with regard to field size, spatial information, and spatial coherence. There was a steady increase in field size and decrease in spatial information content with the number of offset clusters. Thus, for example, spatial coherence showed a steep increase as the number of offset clusters increased past

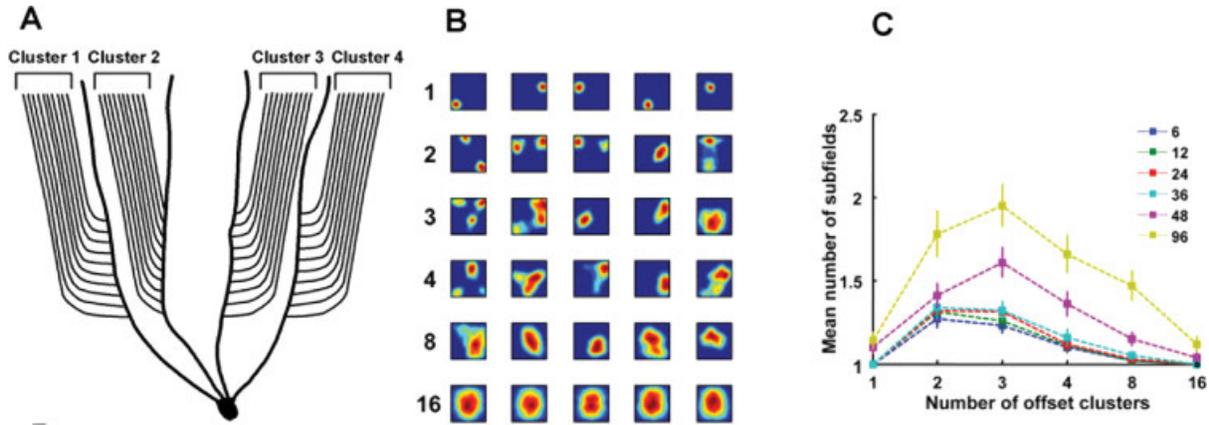


FIGURE 6. The effect of varying the number of offset clusters projecting to each granule cell. (A) Diagrammatic granule cell showing imaginary offset clusters, each comprising inputs terminating on a major branch of the dendritic tree. (B) Five examples of granule cell activation with 1, 2, 3, 4, 8, and 16 offset clusters, respectively. With only one offset cluster (i.e., all grids lining up in

one region of the environment) the fields are singular, and with 16 the fields are large and dispersed across the whole environment. (C) Graph showing how the number of granule cell subfields varies nonmonotonically with the number of offset clusters, peaking at 3–4 clusters. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

four, reflecting coalescence of the fields into a single field covering most of the environment (Fig. 7). Interestingly, the number of offset clusters was far more influential than number of inputs per cluster: for example, an eightfold increase in the number of offset clusters combined with an eightfold decrease in inputs per cluster (keeping total inputs constant) produced an approximately threefold change in the three parameters, whereas an eightfold increase in the number of inputs per cluster produced less than a doubling of the parameters, even with the large change in general number of inputs. Thus, the spatial organization produced by the clustering proved to be important in affecting spatial response characteristics.

The final step was to propagate the activation in dentate through to the CA3 layer, to see whether realistic place fields would be generated. The model granule cells were connected to a CA3 layer by selecting correlated inputs (those with overlapping place fields) by the procedure described in the Methods and diagrammed in Figure 5. Each CA3 cell received inputs

from between three and eight granule cells. The results of this are described below, after induction of remapping.

Inducing Remapping of Granule Cells by Changing the Context

We suppose that when the context is changed, the drive from lateral EC also changes, thus activating a different portion of the dentate dendritic tree and enhancing the drive from a different subset of grid cells. We modeled this by changing one, two, three, or all four of the offset clusters, a manipulation akin to changing some or all of the elements of a compound context [e.g., as in the remapping experiment by Anderson and Jeffery (2003)]. We assessed the effects of the change by correlating the granule cell activation maps. The effects of this manipulation are shown in Figure 8.

It can be seen that there is a steady increase in the degree to which a remapped dentate map differed from baseline with a

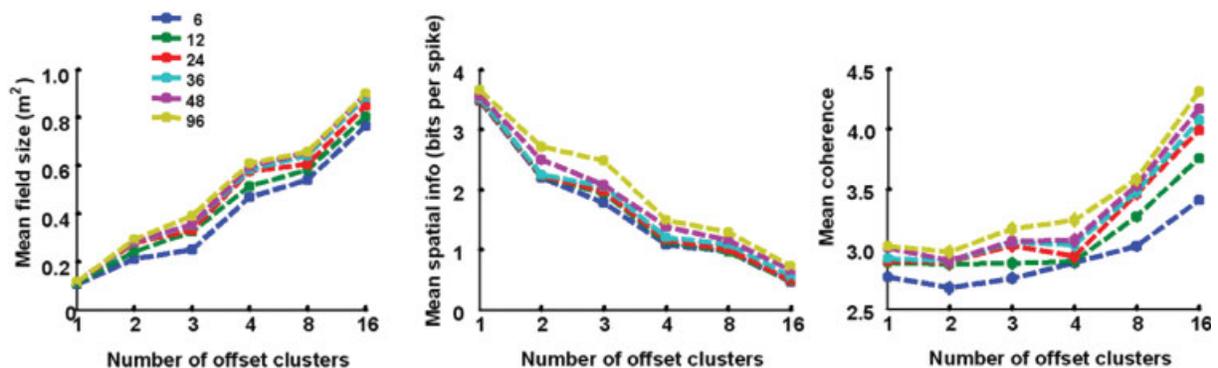


FIGURE 7. Effect of varying the number of offset clusters on field size, spatial information and spatial coherence. The curves are shown for varying numbers of inputs per offset cluster (shown as color codes). Note that the effect of changing offset clusters is

much greater than the effect of changing inputs within a cluster, highlighting the importance of the spatial information conveyed by the clustering. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

change in one, two, three or four offset clusters. Correlations decreased steadily as the number of changed offsets increased, with values (mean \pm SEM) of, respectively, 0.64 ± 0.02 , 0.40 ± 0.03 , 0.26 ± 0.03 , and 0.10 ± 0.03 (shown graphically by the steady progression in the correlation maps from mostly warm to mostly cool colors). Inspection of individual granule cell rate maps revealed some interesting effects. Sometimes subfields seemed to remap relatively independently, which is an effect also observed by Leutgeb et al. (2007) (see Fig. 9). Sometimes individual subfields switched on or off completely, and sometimes they seemed to “move”—all effects that are seen in place cell remapping.

Inducing Remapping of CA3 Cells by Changing the Context

Contextual remapping was then propagated to CA3 by the method described earlier, in which clusters were formed based on correlated activity contributed by both maps (see Methods for details). CA3 maps were then generated using the input configuration thus generated. Figure 10 shows how each set of correlated dentate maps produces a corresponding CA3 activation pattern. Note that because the dentate maps had been generated from both contexts, their fields do not always line up perfectly in one of the conditions. Note also that the activation pattern contributing to the two CA3 fields are, of course, different (because the granule cells remapped), even though the afferent granule cells are the same in both cases.

CA3 maps were compared before and after the context change. Figure 10 shows the effects of changing the inputs: cells in the CA3 layer reacted to the context change by either switching on or off, or by shifting their fields—in other words, they partially remapped. As with the dentate maps, the CA3 maps showed a steadily decreasing correlation with one, two, three, or four offset clusters being changed: with a mean \pm SEM of, respectively, 0.70 ± 0.03 , 0.34 ± 0.03 , 0.22 ± 0.03 , and 0.08 ± 0.03 .

The conclusion is therefore that changing a portion of granule cell inputs can produce partial changes in the CA3 output, and thus our model can explain partial place cell remapping even when the underlying grid cell activation is stable.

DISCUSSION

In this article, we have proposed a mechanism by which spatially heterogeneous place cell phenomena, including incomplete remapping, could arise from their spatially (relatively) homogeneous grid cell inputs. We have proposed a model of context-specific modulation of the grid cell inputs into the hippocampus, in which context-related information from the lateral EC terminates in the distal branches of the dentate granule cell dendrites, and acts cooperatively with spatial (grid cell) inputs terminating in the middle third. According to our proposal, incoming grid cell inputs are switched on and off by

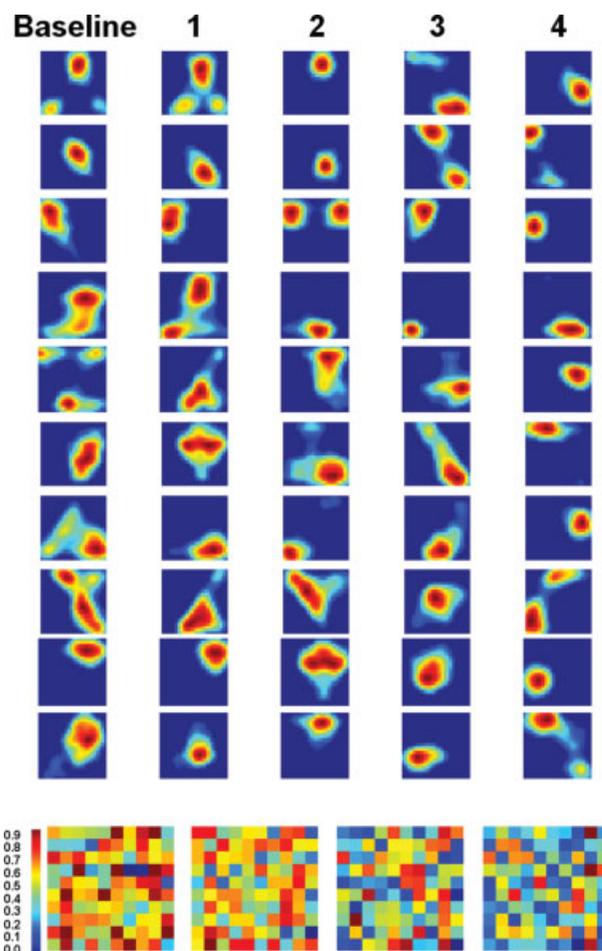


FIGURE 8. Effects on granule cell activation patterns of varying one, two, three, or all four offset clusters. Correlations between the baseline map and each of the four remapping conditions are shown by the colored panels at the bottom, with warm colors indicating high correlations and cool colors indicating low. Correlations become progressively weaker as the number of altered offset clusters increases. Interestingly, this was manifested in the activation maps as partial remapping, sometimes at the level of individual subfields. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

coincident contextual inputs via cooperative interactions in the dendritic arbor, so that in different contexts, different grid cells drive the granule cells and different fields are expressed.

In constructing a model of this scheme, we found that more realistic granule cell fields were produced if the inputs to a given granule cell had a degree of spatial clustering, thus constraining the spatial phases, or “offsets,” of the grid cells to be only a few. We found that in varying the number of offset clusters, the number of subfields produced in the DG cells peaked at 3–4 offset clusters and just under two subfields (Fig. 6), which produces an interesting correspondence with the data set published by Leutgeb et al. (2007) showing an average subfield no. of 1.7.

We propose that this offset clustering occurs by Hebbian interactions (which we did not model here) occurring between neighboring inputs on the dendritic tree. These would result in

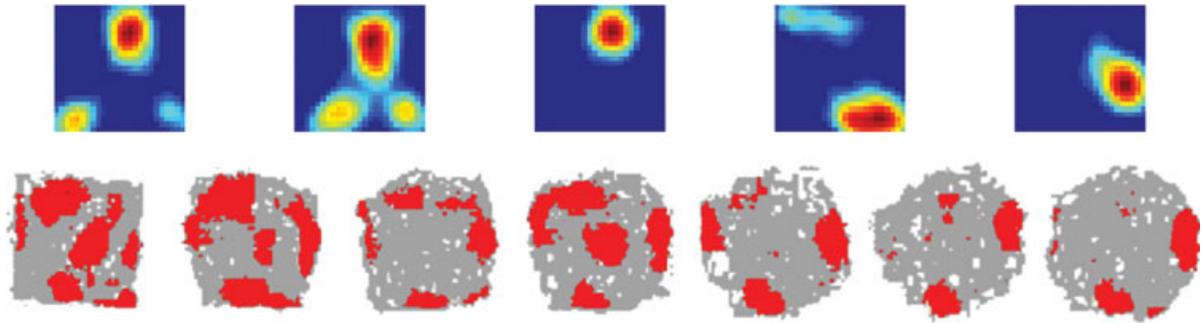


FIGURE 9

**Baseline condition
(4 offset clusters)**

**Remapped condition
(2 offset clusters changed)**

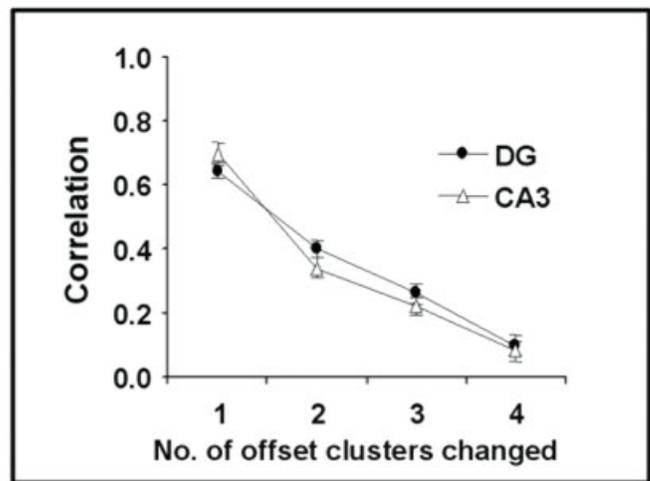
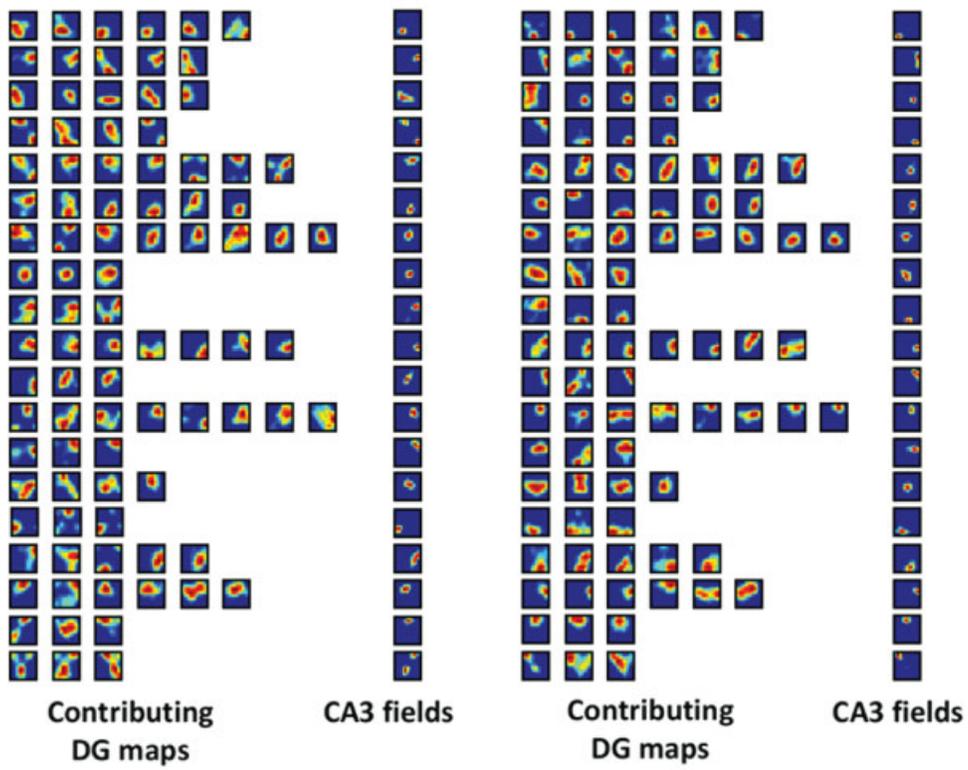


FIGURE 10

spatial clustering of these inputs onto the dendritic arbor of granule cells, so that inputs coactive in a particular context will come to terminate on the same sub-branch of the dendritic tree, and grid cell inputs converging on that sub-branch will tend to have overlapping fields. Based on the morphology of a typical granule cell (Fig. 3), we suppose that one of these “offset clusters” loosely corresponds to one of the main sub-branches of a granule cell dendritic arbor, of which there are typically only a few (Claiborne et al., 1990). Such clustering of inputs onto dendrites has theoretical precedents (Mel, 1993), and is consistent with a growing appreciation of how dendritic morphology affects the processing capabilities of dendritic trees (Sjöström et al., 2008).

Contextual gating of these spatial inputs was then added in three ways—two that could be thought of as “organizational” and one as “activational,” as follows:

1. Organizational. The spatial clustering of the grid cell inputs that seems necessary to make the dentate fields inhomogeneous and punctate was hypothesized to have been caused by coactivity with oncoming contextual inputs.
2. Also organizational. The contextual inputs to the outer branches of the dendritic tree were, in turn, assumed to have become clustered by coactivity such that in a given context, some offset clusters would be preferentially facilitated, and depolarization thus assisted in spreading to the cell soma.
3. Activational. In a given context, active inputs coming in to the distal dendritic branch would act cooperatively with spatial inputs terminating on the middle third, so as to contribute to place field generation in the dentate granule cells.

Using these principles, we have created a simple network that successfully reproduces a number of place field phenomena, as discussed below. The phenomena are (1) The sparse, punctate, and irregular nature of place fields, and (2) Partial place cell remapping. Phenomena not arising from the model that remain to be explained are also discussed.

The Sparse, Punctate, and Irregular Nature of Place Fields

First, our model explains the otherwise puzzling fact that grid cells fire in a regular way across all environments whereas

place fields, both in the dentate gyrus and the cornu ammonis, fire only in some environments and in a spatially irregular way. Our proposal of clustering of the spatial inputs introduces an irregular, environment-specific component to the activation.

We did not explicitly model how such clustering could come to be, but we believe that it is feasible because it is a variant of competitive clustering of a kind that is well established in neural networks. We remain agnostic about whether the process is supervised or not. It may be that this kind of clustering could arise spontaneously from feedforward inputs, but equally it might be that some kind of teaching signal, fed back from the hippocampus and arriving on the most proximal part of the dendritic tree, is needed to guide the clustering process. Indeed, the bootstrapping, partially supervised context-specific clustering of spatial inputs might be the main function of this set of synapses, as the network learns about different contexts and how to parcel up the relevant component stimuli. Modeling this process explicitly is a task for future work.

It might be argued that the spatial nature of the input clustering onto the granule cells means that we have put into the model what we are trying to get out of it—that is, we have injected a spatial signal into the inputs in order to generate the spatially specific place cell code. There is some merit in this argument, but since it is well established experimentally that grid cells are in some sense “pinned” to specific places in specific environments, it is inevitable in any model that some kind of input is needed from the external world to, as it were, initialize the system. The advantage of our proposal is that each grid cell needs only one point of pinning, plus a directional signal, for the model to produce the required inhomogeneity. Thus, the spatial information required as an input is minimal, and indeed need not necessarily be “spatial” (in the sense of “metric”). By contrast, models supposing differentiation of individual grid peaks (e.g., Rolls et al., 2006) or feedback from place cells (e.g., O’Keefe and Burgess, 2005) require an extended spatial signal spanning the environment.

There are aspects of place cell activity that our model does not reproduce, but we believe that these could arise from relatively minor additions to the structure. The first is that granule cells show very sparse coding of environments, being silent in most cases (Jung and McNaughton, 1993; Chawla et al., 2005). This could be easily incorporated into our model by assuming

FIGURE 9. Upper panel shows the occurrence, in our model, of remapping at the level of individual dentate subfields. The maps show, from left to right, the effect of changing one, two, three, or all four offset clusters, and it can be seen that with incremental changes, subfields individually strengthen or weaken. Only when all the inputs change does the cell remap completely. The

lower panel shows a similar effect seen in rats [Adapted from (Leutgeb et al., 2007)]. In this experiment the shape of an environment was gradually changed from a square to a circle, and again, remapping seemed to occur at the level of individual subfields. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

FIGURE 10. The activation maps (top) show the CA3 place fields generated from dentate fields. Activation patterns are shown before and after granule cell remapping was induced by changing the “context” (i.e., by altering two of the four offset clusters onto each granule cell). It can be seen that some fields remained apparently unaltered while others changed their locations—this is an

example for partial remapping. The graph (bottom) shows how the correlations between baseline maps and remapped conditions, for both dentate gyrus and CA3, declined steadily as one, two, three, or four offset clusters were changed. [Color figure can be viewed in the online issue which is available at www.interscience.wiley.com.]

sparse contextual innervation of offset clusters, so that a given granule cell only receives sufficient contextual drive to cooperatively activate its spatial inputs in a small number of environments, meaning that the granule cell maps in our figures would be mainly empty. The second phenomenon that neither our model nor any others adequately explain is why place fields tend to be clustered around salient features in the environment (Shapiro et al., 1997; Rivard et al., 2004), especially walls (O'Keefe and Burgess, 1996), and also why the fields tend to be shaped along the contours of such features (Muller et al., 1987; Muller, 1996). We think we could account for this if it is assumed that the offset clusters were themselves affected in this way by salient features. For example, if grid cells receive additional inputs from cells that fire along boundaries, as have been reported in medial entorhinal cortex (Solstad, 2008), then this could cause the organization of offset clusters into elongated forms—for example, elongated. This in turn should propagate through to hippocampus in the form of appropriately deformed fields.

Incomplete Place Cell Remapping

The second phenomenon our model explains is incomplete, or partial, remapping of place cells. Remapping, when place cells alter their firing patterns, has long been thought to reflect recruitment of a new environmental representation in response to altered stimuli. When the environmental changes are large, place cell remapping is complete (affecting all the cells at once) and is accompanied by grid cell changes in the form of translation and rotation of the grids (Fyhn et al., 2007). The first challenge, then, is how to explain why the place field map does not simply translate and rotate by the same amount. The second challenge is to explain partial remapping, in which changes to a subset of the environmental cues cause changes in only some of the place fields. There is no evidence that grid cells can remap only partially, so where does the place field partiality come from?

Our model can explain both of these phenomena, because it introduces a dissociation between the grid cells and the place cells. The contextual gating of the grid cell inputs means that the inputs only reach the granule cell soma under certain contextual conditions, and these can therefore select the pattern of place cell activity that will arise. Interestingly, in our model some of this pattern occurs via remapping of individual granule cell subfields, which is an effect that has also been observed experimentally (Leutgeb et al., 2007). We speculate that the existence of multiple subfields might enable the linking of a given granule cell to more than one CA3 cell, with one of the subfields linking (by virtue of correlated activity) with one input cluster, and another to a different one.

When complete contextual changes are propagated through to the CA3 network, the fields all remap (note that they do not switch on and off—this is because our granule cell population activity has not been sparsified). Most interestingly, when partial contextual changes are introduced, by changing only some of the offset clusters driving a given granule cell, then the CA3 cells also show partial remapping, with some fields shifting and some remaining unchanged. We believe that this is the

first account of partial remapping that also accommodates what is known about grid cell activity patterns (i.e., their symmetry and omnipresence).

An important component of our model is the assumption of prior Hebbian processes creating the clustering of inputs in the dentate dendrites. It follows that impairment of these processes should affect both the generation of place fields and the presence of remapping. In support of our model, McHugh et al. (2007) engineered mutant mice with a deficiency in one of the NMDA receptor subunits in the dentate gyrus, and consequent impaired synaptic plasticity. They found that CA3 place fields in these mice were of poorer quality and—importantly—did not remap even when the context was changed dramatically. We explain the poorer quality of the fields by suggesting that the Hebbian (i.e., NMDA-dependent) process normally responsible for the clustering of coactive grid cell inputs failed to occur, meaning that the inputs to a given granule cell tended to have distributed peaks and thus produce more dispersed place fields. We explain the failure of remapping by assuming, similarly, that the Hebbian clustering of contextual inputs proposed to occur in the outer dendrites also failed to occur, meaning that the mechanism did not exist to switch grid cell inputs between one set and the next.

Predictions of the Model

As well as explaining existing data, the model makes a number of predictions that could, either actually or in principle, be tested experimentally. These are as follows:

1. Activation in the dentate dendrites. It is an essential requirement of our model that in the freely moving animal, there should be cooperativity between lateral and medial entorhinal inputs such that either alone could not drive the cell in the absence of the other—violation of this constraint would falsify the model. This could be tested by selectively inactivating lateral or medial EC and recording from granule cells. Cooperativity between lateral and medial perforant paths has certainly been shown to enhance synaptic plasticity (McNaughton et al., 1978), and so this is a feasible prediction.
2. If our model is correct, there will be situations in which grid cells do not remap but both dentate and CA3 cells do, due to contextual alteration of the mapping between grid cells and dentate cells. There will, however, never be situations in which granule cells remap but CA3 cells do not. Similarly, there will never be situations in which grid cells remap but there is only partial remapping in granule and place cells. This would also falsify our proposal, in which partial remapping occurs in the presence of a stable grid structure and only the grid/granule cell mapping changes.
3. Spatial-temporal clustering of the inputs to granule cell dendrites. We found that the most realistic looking dentate place fields were found by spatially clustering the grid cell inputs, and so it would be expected that in vivo, synchronous activity should be seen within a sub-branch but not between sub-branches. It is not yet possible to test this experimentally, but one way that may become possible in the not-too-distant future

is to optically monitor calcium-sensitive dye activation in dendrites.

To conclude, we have presented here the first model that accounts for the heterogeneity of place field phenomenology in the face of homogeneous grid cell activity, and in particular, for incomplete place cell remapping. We believe that the model is biologically realistic, based as it is on known anatomy, and it accounts for a number of place field phenomena and also makes a number of testable predictions. Future work aims to refine the model so that its wiring can be shown to potentially form naturally rather than having to be hard-wired.

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