COMMENTARY

Integration of the Sensory Inputs to Place Cells: What, Where, Why, and How?

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ABSTRACT: The hippocampal place cells are a highly multimodal class of neurons, receiving information from many different sensory sources to correctly localize their firing to restricted regions of an environment. Evidence suggests that the sensory information is processed upstream of the hippocampus, to extract both angular and linear metric information, and also contextual information. These various kinds of information need to be integrated for coherent firing fields to be generated, and the present article reviews recent evidence concerning how this occurs. It is concluded that there is a functional dissociation of the cortical inputs, with one class of incoming information comprising purely metric information concerning distance and orientation, probably routed via the grid cells and head direction cells. The other class of information is much more heterogeneous and serves, at least in part, to contextualize the spatial inputs so as to provide a unique representation of the place the animal is in. Evidence from remapping studies suggests that the metric and contextual inputs interact upstream of the place cells, perhaps in entorhinal cortex. A full understanding of the generation of the hippocampal place representation will require elucidation of the representational functions of the afferent cortical areas. © 2007 Wiley-Liss, Inc.

KEY WORDS: place cells; grid cells; sensory integration; space; context

INTRODUCTION

Since O’Keefe’s discovery of place cells, in the early 1970s, research attention has been fairly evenly divided between trying to understand what these cells are for and in understanding how their firing properties arise in the first place; that is, in how they determine where they are. Even before their place-specific firing properties were elucidated, it was recognized that hippocampal neurons respond to sensory information arriving from a variety of different modalities (Ranck, 1973). Once it was appreciated that these neurons were interested in “place,” the question arose as to how they could construct a place representation from such varied information. What form does this information take? Is the “placiness” of place cell firing locations (the place fields) inherent in the inputs, or does it somehow arise from the computations that place cells perform? Indeed, is space special to the hippocampus at all, or do place cells just look placey because rats experience spatial stimuli more than they do other kinds of stimuli?

To answer this question it is necessary to have a clear idea of what kinds of information place cells receive, and of what they do with this information once they receive it. The present article reviews data on how place cells integrate their sensory inputs and examines whether these inputs are specifically spatial or whether there is another, superordinate category of description that encompasses both the spatial and nonspatial inputs known to influence place cells.

Adding fuel to the spatial/supraspatial debate has been the emergence in recent years of many reports of nonspatial determinants of place cell activity, raising the question of whether place is really the fundamental correlate of place cell activity at all. Observed nonspatial determinants of place cell activity have fallen into two broad classes. The first comprises those kinds of stimuli which although not strictly spatial (in the sense of “metric”: see below) in themselves, nevertheless may contribute to the fleshting out of a place representation. An example might be the “color” of the environment, its texture, odor, or even (so it now appears) the expectations or intentions of the rat. These stimuli have in common the property of being stable—that is, continuous in time and/or place—and of defining the environment in a way that may assist the animal not only in knowing where it is but also what occurrences to expect there or what actions it should perform. The second class of stimuli is a much more ill-defined and contentious collection, consisting of discrete events such as tone conditioned stimuli (Berger and Thompson, 1978), reward (Breese et al., 1989), shock (Moita et al., 2003), and discrete odor cues (Wood et al., 1999). The degree to which these discrete stimuli modulate place cell activity independently of place is still debated (O’Keefe, 1999), as is their functional significance.

For the remainder of this article, the term “spatial” will be replaced with “metric” to remove any ambiguity about what is meant by this class of stimuli. As described further in the next section, “metric” refers to some kind of distance measure, either linear or angular. Thus, by “metric inputs” to place cells is meant “inputs to carrying information about distance and/or direction”. Nonmetric inputs are those that do not carry such information. It will be argued that there exists a
functional and anatomical dissociation between metric inputs and (what we shall call) contextual, nonmetric inputs with the former being selected, or “gated”, by the latter. The article will conclude that evidence supports a functional differentiation of spatial vs. nonspatial inputs to dorsal hippocampus, with spatial inputs being primary.

## METRIC INPUTS

A metric, in mathematics, is defined by the *Oxford English Dictionary* as the “binary function of a topological space which gives, for any two points of the space, a value equal to the distance between them, or a value treated as analogous to distance for the purpose of analysis.” The critical thing about a metric is thus that it provides, by one means or another, information about the distances between two identified points in a given space. For place cells, “distance” is taken to mean either “Euclidean distance” or “angular distance.” In the case of a rat in a recording box, this information might consist of information determining how far apart (in Euclidean space), say, two place fields are.

Although place fields undeniably occur in specific regions of space, it was never a foregone conclusion that these locations should be specified metrically. They might be specified by some nonmetric means: for example, by some conjunction of cues such as odors, visual cues, or a mixture that only occurs at a particular place. Alternatively they might be determined topologically, so that a given place field would primarily be localized by the fields around it, with preservation of adjacency relationships between all the fields in a given environment, but no explicit representation of distance *per se*. In this case, there would of course need to be some mechanism for anchoring the topological sheet of fields, as it were, to the real world, but this need not be a metric one. However it turns out, as described below, that a growing body of evidence suggests that the environment does indeed provide metric—distance and direction—information. This evidence falls into three main classes, the first weakly circumstantial and the remaining two very strongly supportive of the notion.

1. Place cells are sensitive to metric transformations of the environment.
2. Place cells will accept replacement of one sensory stimulus by another, totally different kind of stimulus, as long as these stimuli are equivalent (or *isomorphic*) in the metric domain.
3. Cells in brain areas afferent to the place cells have angular and linear metric response properties.

### Place Cells Respond Metrically to Metric Transformations of the Environment

The first indication that place field locations might be determined by metric information came from Muller and Kubie’s classic scaling experiment (Muller and Kubie, 1987), in which expansion of an environment was found to cause an expansion of place field size. Interestingly, however, the scaling was not quite proportional, suggesting an influence of other cues than simple environment size.

In a more tightly-controlled test of scaling, O’Keefe and Burgess (1996) manipulated the metric properties of a recording environment—a wooden box—in each of the two dimensions, configuring the recording box as a small square, a rectangle oriented east–west or north–south, or a large square. Because all the box configurations used the same physical walls, the changes were subtle, and so the place cells did not reorganize their firing as they do if large, noticeable changes are made to an environment. Place cells also reacted in a subtle way, usually just shifting their fields slightly. Different cells reacted in different ways, as if not all of the cells were privy to the same information. By and large, fields tended to be most influenced by the walls closest to them so that they “followed” those walls in preference to the more distant ones. Taken together, the data suggested that a given cell processed information primarily from a subset of nearby walls. O’Keefe and Burgess proposed that a given cell was in receipt of metric information from two or more orthogonal walls in the form of a Gaussian tuning curve peaked at a set distance close to each of those walls. A combination of two such Gaussians from two orthogonal walls proved very effective in modeling the way in which the fields reacted to the changes in the environment.

Although the O’Keefe and Burgess model postulated an explicitly metric input to place cells, the stretchy-box results might still be explained by reference to some kind of sensory input from the walls that varies linearly with distance but does not explicitly encode distance (that is, could not in itself be used to perform metric computations such as trigonometry). Arguing against this is the second indication that place field inputs have an explicitly metric component.

### Place Cells Will Accept Replacement of One Sensory Stimulus by Another Totally Different Kind of Stimulus if These Stimuli Are Equivalent in the Metric Domain

It is a now well-established finding that place cells will accept stimulus substitution if the stimuli are metrically equivalent. An example of what this means is shown in the angular domain in Figure 1. A place field, recorded in a rotationally symmetrical environment, “followed” rotation of the visual directional cue, a lighted cue card, irrespective of signals from the rat’s internal sense of direction. If the card was removed so that no visual polarizing landmarks remain, the cells now followed, equally readily, rotations of the rat itself. Thus, the cells can use either a visual landmark or the internal “direction sense” of the rat—both polarizing stimuli—to orient their fields. Similarly, although place cells generally follow visual polarizing cues, in a sloping environment they can use the slope as an orienting cue if the visual cue is removed (Jeffery et al., 2006). This is despite
Having established that place cells appear to receive metric inputs, the question arises as to how the cells integrate these inputs. There are two classes of metric input, directional and linear, and so the relevant interactions comprise directional inputs with each other, linear inputs with each other, and directional inputs with linear inputs. At this stage, the discussion is about purely metric information—the question of how nonmetric information (including that from objects and landmarks) is incorporated into the representation will be dealt with later.

Integration of Directional Inputs With Each Other

Directional inputs are those that provide information about the orientation of the environment, or of the rat within the envi-
Visual landmarks seem to be powerful cues for orienting the place and head direction cells. In the early studies of place cells, it was found that rotation of a prominent cue card within an otherwise rotationally symmetrical environment would cause concomitant rotation of place fields (Muller and Kubie, 1987). Later studies found that cue card rotation also caused head direction cells to rotate their firing orientations (Taube et al., 1990b), and that place cell and head direction cell rotation rarely, if they ever become uncoupled (Knierim et al., 1995; Hargreaves et al., 2007, this issue), leading to the proposition that place fields assume the orientation they do because of the head direction cells. Head direction cells respond better to polarizing visual stimuli that are located at some distance from the rat (Zugaro et al., 2001), and it is assumed that the directional system has evolved to prefer cues that are more reliable indicators of global orientation (distant cues being better because their relative angular position changes little with the animal’s movements).

Relatively little is known about how information from cue ensembles is integrated in the directional domain. In a study using two cue cards, Fenton et al. found that moving the two cards apart by a small amount caused a topological deformation of place fields, with all fields being influenced by both cards to a greater or lesser extent, but a given field being most affected by the card closest to it (Fenton et al., 2000). This is an interesting experiment and raises the question of how head direction cells would react to such a manipulation—would head direction cell firing directions also “pull apart”, or would the representation maintain coherence, as predicted by attractor models of the head direction system (Zhang, 1996)? The latter would necessitate a partial uncoupling of the head direction and place cells, which, although surprising, is not inconsistent with recently reported data from double cue dissociations (Yoganarasimha et al., 2006), in which head direction cell coherence was maintained but place fields dissociated.

Directional cues occur in modalities other than vision. Earlier we discussed two other kinds: movement-based cues (path integration), revealed by slowly rotating an animal in darkness and observing that place fields rotated too, and terrain slope, which provides vestibular and proprioceptive information. Conflict experiments provide useful information about how these different forms of information interact. When vision and path integration are placed in conflict, place cells generally prefer to follow the visual stimulus (Jeffery, 1998). Two exceptions to this rule have been noted. The first is that if the rats saw the cue card move and the movement was large (i.e., introduced a big conflict), the cells are less likely to follow it (Rotenberg and Muller, 1997). The second is that if the rat had previously seen that the cue card could move, then the cells are subsequently disinclined to follow it even if the conflict is now introduced out-of-sight of the rat (Jeffery and O’Keefe, 1999). These experiments show that the place system somehow weights the two sources of information and makes a decision about which is more, as it were, “trustworthy.” Furthermore, this weighting is plastic and can be modified by experience.

It remains to be determined how and where these multifarious sources of directional information are integrated, but it is likely that the above conflicts are resolved in the head direction system, which seems, as far as we can tell, always to generate an unambiguous, holistic directional signal.

**Integration of Linear Inputs With Each Other**

Place fields have a two-dimensional structure, and so their locations must be determined by at least two one-dimensional metric parameters. These might consist of a vector together with the distance from some origin (a landmark, say), and thus take the form of a polar coordinate system. Alternatively, they might consist of two distance parameters aligned orthogonally, and thus comprise a Cartesian coordinate system in which the two alignment directions form a reference frame, analogous to x and y axes. Although a polar coordinate system might seem more intuitive for a biological agent, particularly one known to possess directionally selective neurons, evidence in fact is more supportive of the latter.

Support for the Cartesian hypothesis of place field localization first came from O’Keefe and Burgess’s (1996) stretchy-box experiment, described earlier, in which it appeared that place fields were formed by the intersection of distance inputs coming from orthogonally aligned walls. In an extension of this model, Hartley et al. showed that a similar effect would arise from multiple inputs from irregularly oriented walls (Hartley et al., 2000), and incorporation of plasticity into their model accounts for development of fields with experience (Barry and Burgess, 2007, this issue). The implication is that the underlying coordinate framework is generated by the intersection of linear metrics, rather than combination of a single linear metric together with an angular metric, that is, it is Cartesian rather than polar.

In a test of the polar vs. Cartesian hypotheses, we progressively deconstructed a four-walled recording environment until only a single landmark and a single directional cue remained. The experiment was conducted in near-darkness and the rat was confined to the centre of the room by a “noise boundary” (i.e., it was punished with aversive white noise if it ventured beyond the boundary: Barry et al., 2006). Figure 2 shows what happened when the walls were removed one by one: place fields progressively disintegrated. Although the remaining features carried enough information to uniquely define any point in a polar coordinate-defined space, this information was apparently insufficient to define stable place fields (with the occasional rare exception, see below). This suggests that the coordinate system is not inherently polar.

The wall-removal experiment above provides some support for O’Keefe and Burgess’s boundary vector model, inasmuch as removal of walls caused place fields to break down. It should be noted, however, that in a number of cases a field was able—at least for a short time—to be supported by a single wall, and occasionally, though very rarely, even a single pillar, a finding that remains to be explained.
In an attempt to isolate the individual inputs—the putative boundary vectors—to place cells, an additional experiment was conducted in which one of the walls of the four-walled box was pulled out from the others just enough to let the rat escape into the surrounding room (Barry et al., 2006), thus enabling a comparison of the enclosed space (surrounded by four walls, albeit one slightly separated from the rest) and the open space (each part bounded by a single wall). It was thought that this procedure might uncover the component vectors driving a given place field. In one case it seemed as if this might be so (Fig. 3 Cell 3), but generally, cells were reluctant to fire outside the box, while continuing to maintain their fields inside it. It thus seems that place cells prefer to fire in enclosed spaces. One possible explanation for this is that the boundedness offers more possibilities for summation of inputs to above firing threshold. This is a far from proven hypothesis, however. It may also be that the intrabox field is somehow able to suppress other fields in the connected space outside the box by a nonlocality mechanism discussed later.

Where do the above-described linear metrics come from? In other words, how does a place cell determine how far the animal is from a given boundary? In a familiar environment, much of this distance information may be visual, for example, the animal may know from experience how high the walls are, and thus be able to use their apparent height to infer their distance. In a novel environment, however, or in darkness, it must be able to use something else. A great deal of evidence now suggests that this "something else" comprises movement cues generated as the animal moves through space; this is the process of "path integration" referred to earlier [see (Etienne and Jeffery, 2004), for review]. Path integration has been shown to influence metric integration in the linear domain, and this was initially suggested by the well-established observation that place fields persist in the absence of vision (Quirk et al., 1990; Save et al., 1998). It was shown explicitly by Gothard et al. (Gothard et al., 1996), who recorded place cells as rats shuttled on a linear track and found that fields were determined by the closest wall, even if this was the one behind the rat. However, it was not until the discovery of grid cells (Hafting et al., 2005), however, that the importance of path integration as the basis of the hippocampal metric really became established beyond doubt, because it seemed that the constancy of the grid cell metric across environments could only be established by an internal, movement-based process. In other words, because the grid spacing of a grid cell occurs at its charac-

![Figure 2](image1.png)

**FIGURE 2.** Degradation of place fields as their metric determinants are progressively removed. (A) A four-walled environment was deconstructed, wall by wall, until only a single wall remained. The quality of the place field steadily deteriorated too. (B) For a population of cells, place field quality, as measured by compactness (are over which the cell fired, left) and coherence (degree to which the cell's activity was concentrated in one place, right), was related to the number of walls in the arena. This supports the notion that place fields are determined by summation from boundaries, rather than from polar-coordinates requiring only an origin and a direction. Adapted from Barry et al., 2006.

![Figure 3](image2.png)

**FIGURE 3.** Recording of three place cells in a closed (left maps) and a surrounded but slightly open (right maps) space defined by four walls. Place fields tended to be compact within the bounded area. When the south wall was moved to allow the rat to escape into the surrounding area, the cells continued to fire as strongly or even more strongly within the bounded region, and only occasionally was a field seen in the unbounded region (e.g., Cell 3). This observation supports the boundary summation hypothesis of place cell integration. Adapted with permission from Barry et al., Rev Neurosci, 2006, 17, 71–97, © Freund Publishing House.
teristic spatial frequency even in a never-before-visited environment, and even in the dark, this spacing could not be determined by static environmental cues (which are arbitrary, and unique to a given environment) but only by dynamic, motion-derived information (which is constant for all environments).

Despite the evident importance of motion-derived cues for establishing a grid cell’s grid, there is now overwhelming evidence that the grid cell firing pattern in a familiar environment must arise from a learned interaction between the internal metric and environmental cues. Some of this evidence was presented by Hafting et al. in their original report, in which they showed that rotation of a cue card caused a concomitant rotation of the grids. This reveals landmark control for the angular domain, at least. The fact that grids in repeated trials always have the same offset with respect to the environment also implies some kind of anchoring process that aligns the grids to the environment in the same way upon repeated trials. Another clue comes from the observation that the grids tend not to be perfectly regular, and that the irregularities also persist across trials, suggesting that a given peak in a grid is somehow uniquely specified in a given environment.

That this anchoring is learned, rather than hard-wired, has now been shown by an experiment of ours (Barry et al., 2007) in which grids that were established in an environment of one size were able to be deformed (or “rescaled”) by subtle changes in the dimensions of the enclosure (Fig. 4). This rescaling could be induced in either direction: if the rat was familiarized with a large square enclosure, compression of one of the axes to form a rectangle caused a partial compression of the grid in that axis; conversely, if the rat was familiarized with a rectangle, expansion along the short axis to form a square caused expansion of the grid ion that axis, but not the other. Because the rescaling was only partial, the implication is that deforming the environment sets up a conflict between the intrinsic path integration metric and the extrinsic learned boundary cues. Understanding how both intrinsic and extrinsic cues can influence grid spacing in tandem like this is a current priority.

Integration of Directional and Linear Inputs

Regardless of whether the coordinate system employed by place cells is polar or Cartesian, it is necessary for there to be some kind of integration of directional and linear inputs. In the polar case, this is because direction is one of the two components of the vector identifying locations, and in the Cartesian case it is because identical walls can only be distinguished on the basis of their directions. Additionally, the finding that place cells can “path integrate” in order to update their position calculations indicates that somewhere, angular and linear distance information must be processed together.

The head direction cells are the obvious source of directional information to place cells, but because the head direction areas do not project directly to the hippocampus, it has always been understood that there must be some mediating structure. It now seems likely that the grid cells are the site of this mediation. Grids have a clear and reproducible orientation in a specific environment (Hafting et al., 2005) and are in receipt of direct inputs from head direction areas. In addition, many grid cells, most prominently in the deeper layers of entorhinal cortex, have directional firing properties, and many straightforward head direction cells are also found in these areas (Sargolini et al., 2006). Most intriguing of all, inactivation of hippocampus, which feeds back into the deep layers of entorhinal cortex, causes some grid cells to lose their grids but retain their directionality, becoming in effect, head direction cells (Bonnevie et al., 2007). These findings point to the importance of directional information in the grid cell network and support the notion that that linear and angular information are combined here and passed thence to the place cells.

The foregoing discussion focused on how place cells integrate the various sources of information that specify where a place field should be located. However, as noted earlier, a growing body of evidence points to the responsiveness of place cells to nonmetric inputs. Are these inputs of a qualitatively different kind, or are both metric and nonmetric inputs merely variants of some other kind of superordinate category of information? For reasons of
Clarity and conciseness, we shall refer to the nonmetric inputs, discussed in this section, as "contextual".

Modulation of spatial activity by nonspatial cues is manifest as the phenomenon known widely as "remapping," an example of which is shown in Figure 5. Remapping occurs when a highly salient change is made to an environment, and was originally considered to reflect recruitment of a new environmental representation (Muller and Kubie, 1987). In classic, so-called "complete" remapping, all cells alter their activity simultaneously, some stop firing, some previously silent cells develop fields and some, about 50%, lose a field in one place and develop a new one in a different place. More recent reports have suggested that the distribution of on-off vs. location-shift remapping differs depending on where the cells are located, with CA3 cells more likely to on-off (or "rate") remap and CA1 cells more likely to shift their fields (Guzowski et al., 2004; Leutgeb et al., 2004). The question remains open as to whether these are qualitatively different phenomena.

Remapping can be induced by a variety of different kinds of environmental change, including changing the color of a cue card (Bostock et al., 1991), the shape of the box (Lever et al., 2002), color and odor of the box (Anderson and Jeffery, 2003), or placing the recording box in a new place (Hayman et al., 2003) or room (Leutgeb et al., 2004). It can, however, also be elicited by a different kind of stimulus such as changing the task the animal is performing in a given chamber (Markus et al., 1995) or changing the route it is traveling (Wood et al., 2000; Frank et al., 2000). These are particularly interesting because they do not involve making physical changes to the environment—the change is all in the mind of the rat, so to speak. We shall refer to these classes of stimuli as "external" and "internal," respectively.

**Contextual Stimuli External to the Animal**

External stimuli known to invoke remapping are those that cause some kind of salient, easily sensed change to the environment. Some kinds of environmental change invoke complete remapping, i.e., change to the whole observed place cell population simultaneously, whereas others involve only some cells (partial remapping). Initial studies of remapping looked mainly at complete remapping. The strong sense of observers that the place cell network was "flipping" into a new state during this process prompted the development of attractor-based models (Samsonovich and McNaughton, 1997; Tsodyks, 1999) to explain the sudden, network-wide transition in activity patterns. In attractor models, the assemblage of incoming sensory data is shared among neurons in the highly interconnected CA3 network and eventually settles to a stable state, specific to that environment and generating a unique pattern of activity across all place cells. By this view, because an individual CA3 neuron gets most of its inputs not directly from sensory sources, but rather, from other hippocampal neurons (Amaral and Witter, 1989), the sensory correlates (such as responsiveness to particular cues) arise as emergent phenomena from network processes, rather than from direct sensory drive. More recent findings of partial remapping (e.g. Anderson and Jeffery, 2003) challenge this view somewhat, because they require at least two networks of neurons (in some cases four), one of which remaps and the remainder which do not, in each one of the environments.

The conditions under which partial vs. complete remapping occur have not yet been defined. Our experience is that even in a given environment with a given protocol, remapping patterns can vary, sometimes frustratingly. The likely reason is that because remapping is the output of network computations, relatively small changes in parameters, including animal-specific variations, can affect whether the system responds to the stimuli or not. One such parameter is probably how salient the stimuli are initially. If a context change is made highly salient by using more than one cue (e.g., shape combined with color), remapping will subsequently still occur even if the context change is now restricted to just one of those cues (Wills et al., 2005). One interpretation of this is that the initially salient changes enable the network to carve out two attractor basins after which the system more easily settles into one of these basins when nudged by just one of the original cues. However, stimulus salience cannot be the only factor, because we have observed that highly salient stimuli (as ascertained by the reaction of the rat; for example, rearing in response to a strong odor) do not always cause remapping (Caswell Barry, unpublished data). Another factor may be how familiar the original environment was before the contextual

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1Rats have essentially monochromatic vision and so the visual stimuli in the experiments described here have always involved variants of black, white and grey. Strictly speaking, these are not "colors," they are degrees of brightness, or luminance. However, the term "color" is used here because it is a term we more usually use to describe wall and floor coverings. If the reader is offended by this mild inaccuracy then please mentally replace "color" with "brightness" throughout.
change was made: in a familiar environment a change may be surprising, perhaps attracting attention from the rat. Indeed, there is some evidence that attention may be a factor in whether stimuli induce place cell changes (Kentros et al., 2004).

It is worth noting here that although a distinction has been made above between metric and contextual cues, this distinction may not be clear-cut; it may be that metric cues can also act as contextual cues under some circumstances. An obvious example is the two-box-location experiment of Hayman et al. (2003), in which place cells remapped when the recording box was translated between a north and south location. Although the change made was a spatial one, it could be that the effect was to change the contextual aspects of the environment. We draw this conclusion because place fields never appeared to be dragged around within the box by the environment translations (by analogy with how they were dragged by walls in the O’Keefe and Burgess 1996 experiment); rather, they either remained in the same location relative to the box or switched on and off. A similar space-as-context explanation may account for the findings of Lever et al. (2002) that changing the box from a circle to a square caused sudden transitions between states.

**Contextual Stimuli Internal to the Animal**

As mentioned earlier, another kind of stimulus can induce remapping; these are stimuli that are not properties of the physical environment per se, but rather are more abstract stimuli, such as the task the animal is performing at a given time (Markus et al., 1995) or which of two overlapping routes it is currently executing (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003). These kinds of stimuli are particularly interesting because they are not detectable to an observer and must not therefore arrive at the hippocampus via a simple sensory route. Because these observations have been made when the animals are performing highly repetitive tasks, some observers have considered that the salient features of the stimuli are their sequential nature: that is, the cells are considered to be responding to temporally organized sequences of actions, and are thus perhaps encoding a simple form of episodic memory (Wood et al., 2000; Shapiro et al., 2006). An alternative viewpoint, however, is that the parameters in these tasks that control remapping are those that could be considered to be a part of the “context”, that is, they are aspects of the environment that are relatively stable, ongoing (albeit switching back and forth), and define it in terms of the actions that must be performed there. By this view, the reason the hippocampus is interested (in the sense of responding to) in these stimuli is because they form a part of the spatial context, or, as it were, the situation the animal is in. In support of the latter characterization, remapping to task parameters is a fickle phenomenon and does not always occur in situations where the rat is clearly executing a task with sequential components (Lenck-Santini et al., 2001; Bower et al., 2005). By the contextual-encoding view, the fickleness arises from the likelihood that for whatever reason, some conditions favor the formation of two attractors to represent the context, and other superficially similar ones favor only one. The finding that internal factors can cause environment-specific remapping leads to the notion that the hippocampal encoding of “place” is highly multidimensional, extending far beyond the mere physical layout and metric parameters thereof.

**INTEGRATION OF CONTEXTUAL INPUTS WITH EACH OTHER**

Because “context” is such a multifarious phenomenon, the question of interest regarding integration of contextual inputs is whether this integration occurs upstream of the hippocampus, implying a “context processor” somewhere in the neocortex, or whether the place cells themselves are the site of contextual integration. This is important for understanding how the fully fleshed-out place representation is ultimately constructed.

We explored this issue by creating multielement contexts (each a “color” paired with an odor) and observing remapping patterns to determine whether the cells would respond to the contexts en bloc, which would suggest that the inputs had already been integrated upstream, or whether they responded to the elements individually (Anderson and Jeffery, 2003). We found the latter; that is, the place cells responded heterogeneously to the contexts, each responding to some unique color/odor combination. The implication is that rather than receiving a preprocessed, holistic context signal, the contextual information must have arrived at the place cells in elemental form, to be combined in the hippocampus.

It seems that place cells are not hard-wired with (all of) their contextual inputs: these can be learned. In a pilot experiment in which a box enclosure was moved back and forth between two locations, place cells acquired the ability to discriminate the locations over repeated trials spanning several days (Jeffery, 2001). This discrimination, which we take to be a contextual discrimination (for reason discussed earlier), was subsequently found to show a second-order context specificity, inasmuch as the contextual discrimination occurring in one context (e.g., a black box) did not transfer to another context (a white box; Fig. 5) (Hayman et al., 2003). The context-specific behavior (where “context” is location) was itself context-specific (where “context” now means color). Our interpretation of this surprising finding is that the inputs enabling the place cells to discriminate contexts in the locational domain were themselves selected by the inputs in the color domain. This implies an interaction between the contexts – location and color – upstream of the place cells.

**INTEGRATION OF METRIC AND CONTEXTUAL CUES**

How do metric and contextual cues interact and where? Is there a reason to think these kinds of stimuli are functionally different?

Although both metric and contextual cues influence place cells, the phenomenology of their responses to contextual and
metric manipulations suggests that the nature of this influence is different. Whereas variation of metric cues (by virtue of the animal’s walking around in the environment) causes a steady increase or decrease of firing rate as the animal moves into and out of a place field, variation of contextual cues often causes an abrupt, discontinuous change (“remapping”): the cells start or stop firing or the place field jumps from one part of the environment to another. It could be argued that these different behaviors merely reflect the different way in which metric vs. nonmetric cues vary in the real world. An animal is able to experience smoothly varying metric cues because it locomotes smoothly around the environment, whereas it usually only experiences contextual changes in a sudden way. Perhaps, if we were able to smoothly vary contextual cues, we would see that place cells respond smoothly in the contextual dimension too. By extension, perhaps, as far as the hippocampus is concerned, contextual cues are no different from metric cues.

Over the past several years we have begun to explore the issue of whether contextual and metric cues are functionally dissociable, and our impression is that they are. In the first such experiment, we looked at the remapping induced when a recording box was changed from black to white (Jeffery and Anderson, 2003). This simple, nonmetric change induced complete remapping, with approximately half of the cells switching off or on and the remainder developing new firing locations, as usual. The latter class of cells, which shifted fields, was especially interesting in this experiment because the cells were expressing different spatial coordinates depending on the box color, which enabled us to test how they might determine which coordinates to use. The question we asked was: why did changes occur to the spatial firing of the cells when the box was changed? Was this because the cells received inputs specifying how far they should fire from black-walls and different inputs specifying how far they should fire from white-walls? In other words, were they receiving “color-coded” metric inputs? This proposition was tested by creating hybrid boxes in which some of the walls were black and some white. We hypothesized that new fields should develop, having hybrid x-y coordinates, so to speak: that is, the new fields should be determined in the x-dimension by walls of the x-color and in the y-dimension by walls of the y-color. Thus, the new fields in the hybrid boxes should be predictable on the basis of knowing the field location in each of the single-colored boxes.

This manipulation was so singularly ineffective that it was quickly abandoned; the fact was that despite their robust remapping to complete color changes, the cells responded little to the partial wall color changes. We made changes to the floor color instead and found that whatever combination of wall and floor color we used, the cells nearly always, with rare exceptions, adopted the place field pattern appropriate to the floor, irrespective of the walls. It is as if the cells did not even receive wall-color information. And yet, they clearly receive wall information of some sort, because place fields will readily follow walls if the walls are moved. The seemingly inescapable conclusion is that place cells use walls and floor differently; they use walls as a basis for computing distances, but the floor to tell them which environment they are in, and therefore which field to express.

On the basis of these, and other, findings, we have proposed a functional distinction between contextual and metric inputs, whereby metric inputs (from boundaries) specify the location of a place field in the manner proposed by Burgess and colleagues (O’Keefe and Burgess, 1996; Hartley et al., 2000), whereas contextual inputs select which of these spatial inputs will be active in a given environment (Fig. 6). By this view, rate remapping can be understood as a variation in the strength of the drive through a given set of metric inputs produced by small changes in context, and “global” (or locational) remapping as when large context changes cause one set of inputs to be silenced altogether (its contextual modulators no longer active at all) and a new set (possibly) activated instead.

The above scheme is an abstract formulation of the underlying logic of the input structure. How might such a scheme be implemented in reality, particularly in light of what we have recently learned about grid cells and their interaction with place cells? An interesting and relevant observation is that although place cells frequently express independent fields in two different environments, such cells tend not ever to express both fields together in any environment. (Note that place cells frequently do have more than one place field; however these always remap together and behave as if they are, in effect, the same field spread across two locations. What place cells don’t seem to express is two independently-remappable fields at once.) It is almost as if two the fields “know” about each other and thus know not to cooccur, and yet, how can a place field in one location be suppressed by another field which, though potentially active in that environment, is not actually active (because the rat is not at that location at that moment)?

A possible mechanism for this, as it were, nonlocality, lies in the grid cells, whose rigid metric spacing means that if a grid cell is firing in one particular place at a given moment, its firing in a different place at a future time is constrained by whether that location also lies on a grid peak. This constrained firing pattern means that distant parts of the environment are, in a sense, connected via the underlying grid structure. Suppose that place fields are formed by the summation of overlaid grids; it thus follows if
How could this grid-conferred nonlocality explain remapping? In a recent experiment, Fyhn et al. found that following manipulations that induced global remapping in place cells, grid cells would simultaneously shift and rotate their grids in concert (Fyhn et al., 2007). On the assumption that the shift in grids caused the shift in fields, an explanation put forward by these authors (see their Supplementary Fig. 12) is that any manipulation that displaced and/or rotated the grids would shift the alignment point, described above, out of the range of the box enclosure and cause the place field to disappear from inside the box. Were that shift simultaneously to move another alignment point into the box, the result would be an apparent shift of the field. By this view, the reason a place cell can never express both its fields at once is that grid cells can only express one grid at once.

Such a scheme could explain complete remapping: explaining partial remapping is a little more complex. In order for only some place fields to respond to contextual changes, there must be some degree of partial selection of the grid cell inputs by the contextual cues, either because perhaps only some grids realign following a partial context change, or because the subset of grid cells that drives a given place cell can be switched (gated) by context cues. Further experiments are needed to untangle these possibilities.

Putting all this together, we can postulate that the metric of the grid forms the metric component of our metric/contextual gating model, and some aspect of the mapping between grid cells and place cells corresponds to the contextual component. The question of how contextual cues drive place cells has thus become a new question—how do contextual cues drive grid cells? Recordings of grid cells in multielement contexts will be needed to answer this question.

REFERENCES


CONCLUSION

This article has argued for the view that metric and nonmetric inputs to place cells are functionally dissociable, with metric inputs specifying where a cell’s field should go, and nonmetric (or “contextual”) inputs specifying whether or not that field should be expressed in a given environment. Metric inputs are integrated from information arriving in a variety of sensory modalities, and it is likely—based on the responses of grids to contextual, metric, and directional manipulations—that much of this integration occurs in entorhinal cortex. Similarly, contextual inputs are also multimodal, sometimes to a high level of abstraction (such as the parameters of a given task) and again, evidence suggests this integration may take place in entorhinal cortex.

If so much integration occurs upstream of the place cells, then what is the function of the place cells themselves? Evidence from grid cell recordings, such as the hippocampal inactivation study of Bonnevie et al. (2006), suggests that one function may be to provide the anchoring that attaches the grids to the environment. Another function may be to sculpt the attractor basins that underlie the processes of pattern separation and completion postulated to occur in dentate gyrus and CA3. And finally, it may be that place cells provide the combinatorial functions that allow multiple different contexts to be associated with the same set of spatial parameters (Anderson et al., 2006).

While the details of multimodal integration are rapidly being uncovered by studies of place and grid cells, one of the big mysteries is how these neurons contribute to the other function of the hippocampal system, episodic memory. It seems clear that the foundation of the place and grid cell representation is a spatial one, but whether the more detailed and transient parts of a remembered episode are incorporated at this level, or by some other brain region, remains to be determined.


