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REVIEW

Hippocampal place cells are topographically organized, but physical space has nothing to do with it

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Abstract
Topographical organization can be found in many areas of the cerebral cortex, although its presence in higher order cortices is debated. Some studies evaluated whether this pattern of organization is present in the hippocampus, trying to determine whether hippocampal place cells are organized around a topographical map of space. Those studies indicated that the topographical organization of hippocampal place cells is either very limited or simply nonexistent. In this paper, we argue for a different interpretation of available evidence and suggest that there is a topographical organization in hippocampal place cells, but the topographical map formed is not a map of the physical space. Although place cell firing is correlated with the animal's position and is important to spatial navigation, place cells encode much more information than just location. Thus, we should not expect the topographical map to be organized around physical space, but around an abstract, multidimensional space containing the receptive fields of place cells. We show that this conclusion is supported by two of the main theories of hippocampal function–cognitive map theory and index theory–which, when carefully analyzed, make exactly the same predictions about hippocampal topography. Such abstract topographical map would be extremely hard to find using the methods commonly employed in the literature, but there are some approaches that may, in the future, make possible to characterize the topographical organization in the hippocampus and other high-order brain regions.

Keywords Topography · Hippocampus · Spatial navigation · Topographical map · Neural code

Introduction

Primary sensory cortices have the remarkable feature of being topographically organized. In other words, neighboring neurons tend to represent "neighboring stimuli"–like adjacent tones in the auditory cortex or adjacent locations in the field of view in the visual cortex (Patel et al. 2014). This type of organization is made possible by the fact that projections from sensory organs tend to preserve the spatial distribution of the sensory receptors; in other words, the projections are topographically organized as well (Thivierge and Marcus 2007). Thus, if neighboring photoreceptors in the retina receive photons from neighboring locations in the visual field, the successive projections to and from the relays getting the information the primary visual cortex will preserve this spatial organization found the retinal surface.

Although topographically organized projections are found in higher order brain regions (e.g., Mailly et al. 2001), a topographical organization of neurons' receptive fields is not always found (reviewed in Patel et al. 2014). It seems that as we move from primary sensory cortices to multimodal associative cortices and even higher order brain regions, the presence of topography gradually diminishes and the experimental evidence about the presence or absence of topographical organization becomes less clear. So, while we have clear evidence for a continuous map of the field of view in the primary visual cortex, we have (less clear) evidence that indicates the presence of only a discontinuous map with less obvious topographical organization in associative cortices like the lateral intraparietal area and the frontal eye fields (Patel et al. 2014).

The hippocampus integrates multimodal, highly processed information coming from multiple brain areas (Knierim 2015). It is, therefore, no surprise that the quest to find a topographical organization in the hippocampus

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returned conflicting results. Research on the hippocampal topography focused mainly on the receptive fields of place cells–neurons whose activity is correlated with the animal's position in the environment. When looking for a correlation between the place in which the neurons fired and the neuron's location in the hippocampus, some studies found evidence for a limited topographical organization, present only within small, distributed clusters of neurons (Eichenbaum et al. 1989; Hampson et al. 1999; Takahashi and Sakurai 2009; Nakamura et al. 2010), while other studies found no evidence of topography whatsoever (Redish et al. 2001; Dombeck et al. 2010). The situation is complicated by the fact that different studies employed different methods to access the presence of topography. In general, studies provide a stimulus (usually some behavioral test) and evaluate the response of hippocampal neurons. The problem is that, although studies have the same general setup, different studies used different behavioral tests which provide different stimuli to the animals (e.g., delayed nonmatching to sample in Redish et al. 2001, and a spatial navigation task in Eichenbaum et al. 1989) and employed different methods to measure neuronal activity with different temporal and spatial resolutions (e.g., calcium imaging in Dombeck et al. 2010 and immediate early gene expression in Nakamura et al. 2010).

Despite their many differences, the studies as whole point to the conclusion that if there is any topography in the hippocampus, that topography is very limited. In other words, neurons representing neighboring locations in the environment do not necessarily occupy adjacent locations in the hippocampus. As in other high-order brain regions, it is interesting to contrast the apparent absence of topographical organization in the receptive fields of hippocampal place cells with the fact that hippocampus receives topographically organized inputs (Witter 1993; Tamamaki and Nojyo 1995) and preserves this topographical organization of projections between its subregions (Brivanlou et al. 2004). Indeed, it seems that anatomical and physiological evidence form an odd couple in the case of hippocampal topography, even if they are not necessarily in contradiction.

A crucial point in the studies of hippocampal topography is that all of them looked for a topographical organization centered on a spatial map of the environment. In the sections that follow, we will show that this approach was bound to fail in finding a topographical map in the hippocampus, and we will do so by providing a different view of the problem of topographical organization in the hippocampus. We will start with some considerations about the caveats of studying neural representations, and by extension topographical organization, in high-order brain regions. We will then show how those caveats apply to the study of topography in the hippocampus. By highlighting the distinction between the stimulus encoded by a neuron and the information that can be decoded from that neuron's firing pattern, we will show how the two most widely used frameworks for the studying hippocampal function–the index theory and cognitive map theory–come to the exact same conclusions about hippocampal topography. We suggest, based on anatomical and physiological evidence, that there is a topographical organization in hippocampal receptive fields, but it does not form a spatial map of the environment. In other words, the topographical map is there, but is not the map we have been looking for.

Finding what to look for

To understand the topographical organization of any brain region, we must first understand which stimuli are being represented by neurons in that region. It would be really hard to characterize the tonotopic organization of the auditory cortex without knowing that the neurons there respond to sounds in different tones. However, how do we find out what stimuli are being encoded by the firing of a given neuron? The general approach to solving problems of this kind is to present animals with a stimulus or a series of stimuli and measure the activity of the neuron or neurons we are interested in. The nature of the presented stimuli may be chosen based on knowledge about the anatomical connectivity of the region under study. This approach was extremely successful in the case of neurons in primary sensory cortices, and one has to look no further than the classical experiments of Hubel and Wiesel to find an example of such success (Hubel and Wiesel 1962; but see de Vries et al. 2018). Nonetheless, the caveats of this correlational approach become evident as we move from primary sensory cortices to higher order cortical regions (for interesting discussions on this topic, see Quian Quiroga and Kreiman 2010, and Jonas and Kording 2017).

Neurons in high-order brain regions usually integrate information from multiple sources and thus tend to encode rather abstract stimuli composed of multiple sensory and task-related variables (Panzeri et al. 2015). In such cases, the interpretation of correlations between a neuron's firing and the stimuli presented to the animal becomes a treacherous task. To illustrate this point, consider a simple network composed of two layers with 10 neurons in the first layer and 2 neurons in the second layer, with each neuron in the second layer receiving projections from 5 neurons in the first layer (Fig. 1a). Suppose that the two neurons in layer II fire whenever 3 of their 5 inputs are active. Therefore, if only 3 neurons in layer I are active at any given time, then each neuron in the second layer can fire in response to 10 different patterns of stimulation (from 60 possible ways to sample 3 out of a population of 5 with 6 permutations for each triplet).

Suppose a researcher is studying the network in Fig. 1a and wants to find out the stimuli encoded by the neurons

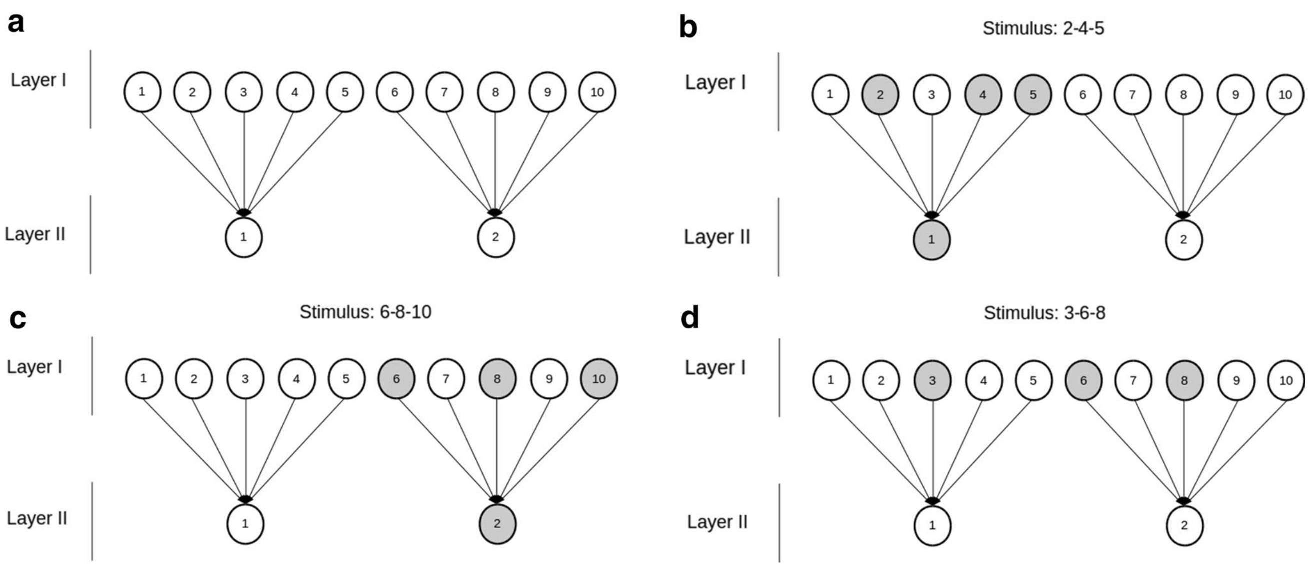

Fig. 1 Here we present a very simple network to be used in a small thought experiment. **a** The network has two layers, the first one having 10 neurons and second having 2 neurons. Half of the neurons in Layer I project to each neuron in Layer II. Give that only 3 neurons in Layer Iare activated by each stimulus provided to the network, then there are three broad categories of stimuli, **b** some stimuli will lead to the activation of neuron 1 in Layer II, **c** other will lead to the activation of neuron 2 in Layer II and **d** and still others will activate neither neuron in Layer II

in layer II. The researcher uses a set of 30 different stimuli, with each stimulus leading to the activation of 3 neurons in layer I (e.g., Fig. 1b–d). Given that each stimulus activates 3 of the 10 neurons in layer I, it follows that there are 120 possible stimuli (from 720 ways to draw a sample of 3 from a population of 10, with 6 possible permutations for each triplet). Since the number of possible stimuli is far greater than the number of stimuli to be presented in the experiment, and that each of the two neurons in layer II respond to 10 different stimuli, it is clear that the conclusions of the researcher about what stimuli are encoded by the neurons in layer II will depend on the identity of the 30 stimuli selected for presentation to the network.

The example above was unrealistically simple–a single neuron in a brain region like the hippocampus can receive thousands of synaptic inputs. However, the example illustrates three crucial caveats with the study of high-order brain regions:

1. Neurons in such brain regions do respond to more than one variable. The stimulus a neuron responds to is usually a combination of simpler stimuli that are integrated by the neuron;
2. There is an enormous amount of possible combinations of stimuli to which neurons in any such neuron would respond;
3. No experiment will be able to present all such stimuli to the animal.

Moreover, in real situations the stimuli presented to the animals are complex ones (e.g., the ones the animal experiences during a behavioral task), so even when a neuron fires in response to a stimulus, it can be hard to assert what features of the stimulus are causally related to the neuron's firing. It follows that the interpretation of results from correlational approaches trying to identify the receptive fields of neurons in high-order brain regions is inevitably limited (see Jonas and Kording 2017, for more on this topic).

If our ability to know what is being encoded by the neurons in a given brain region is limited, then so should be our ability to determine the presence of topographical organization in that given region. At this point, we must stop and ask: what information is being represented by hippocampal neurons? The information represented by any brain region depends on the synapses it receives and is always tightly connected to that region's function. Therefore, to understand what is being represented by hippocampal neurons, it is helpful to recap the general features of the hippocampus and look at the current theories for its function.

The hippocampus and its function

The hippocampus receives highly processed sensory information via the entorhinal cortex (EC). It also receives, either directly or via the EC, projections from multiple brain regions, including the prefrontal cortex, the amygdala, the ventral striatum and the hypothalamus (Teyler and DiScenna 1985; Knierim 2015). As such, the hippocampus is believed to participate in episodic memory by binding together the information it receives about the many facets of particular episodes. The hippocampus is widely believed to function as an autoassociator network, capable of rapidly binding ensembles of neurons together through synaptic plasticity, particularly long term potentiation (LTP) (McNaughton and Morris 1987; Treves and Rolls 1994; reviewed by Kesner and Rolls 2015). Such binding is made possible by the many recurrent connections between CA3 pyramidal cells and would allow for pattern completion, where the reactivation of part of the original ensemble leads to the reactivation of the rest of the ensemble (Marr 1971; Kesner and Rolls 2015). The capacity of reactivating ensembles, aligned with its reciprocal connections to many cortical and subcortical areas, allows the reactivation of ensembles related to specific episodes in many brain regions, forming the basis for memory recollection. The replay of ensemble sequences from specific episodes during sleep (Wilson and McNaughto 1994; Nádasdy et al. 1999) and wakeful rest (Davidson et al. 2009; Karlsson and Frank 2009) can strengthen the connection between the cortical ensembles representing that memory, a process known as systems consolidation, which creates a memory trace in the cortical areas (Kumaran et al. 2016). All of this is common-place in the neuroscience literature but does not explain what is actually being represented by neurons in the hippocampus.

There are many theories available that address the question of “what is represented by hippocampal neurons?”, but two (non-mutually exclusive) theories stand out providing the most widely accepted frameworks for understanding hippocampal function and the nature of its representations: the “index theory” and the “cognitive map theory”. Since both theories make assumptions about what is being represented by hippocampal neurons, both theories have implications hippocampal topography–whether it exists and, if so, what should it look like.

Index theory, developed by Teyler and DiScenna (1986), proposes that the hippocampus serves as an index of neocortical locations. In this view, the function of the hippocampus is to reinstate patterns of activity in the neocortex, which is made possible the mutual connections between the hippocampus and the neocortex, as discussed above. As such, index theory proposes that what is represented in the hippocampus is not the information about the episode per se—hippocampal ensembles, in this view, are “memory trace[s] with no content” (Teyler and Rudy 2007). Instead, what the hippocampus represents are the locations of other brain regions—an index. Crucially, the theory is based on the fact that projections to and from the hippocampus are topographically organized (Witter 1993; Tamamaki and Nojyo 1995), and it predicts the existence of a topographical organization in the hippocampus, an organization related to mapping of neocortical locations (Teyler and DiScenna 1985, 1986; Teyler and Rudy 2007). The exact characteristics of this topographical organization are not specified by the authors, but since hippocampal neurons receive projections from multiple locations in the brain, and that each neuron can receive thousands of synapses, the number of possible combinations of inputs that can activate each neuron is enormous. Therefore, hippocampal neurons are expected to have multidimensional receptive fields (reflecting the multiple locations from which they receive projections). Those characteristics guarantee that the topography would be hard to find, as it would present all three caveats for studying high-order brain regions we mentioned earlier. We shall return to this proposed topography later.

The studies trying to find topography in the hippocampus were not conducted within the framework of index theory. They were conducted under the framework of cognitive map theory, which poses that the hippocampus maps the many features that compose different episodes, creating representations that can be used to guide navigation and goal-directed behavior (Tolman 1948; O’Keefe and Nadel 1978; see Moser and Moser 2013, for a modern discussion). Cognitive map theory has been strengthened by the discovery of different types of neurons with place-correlated activity, which reinforced the association of the theory with the idea of a representation of physical space in the hippocampus (reviewed in Moser et al. 2017). The studies evaluating topography in the hippocampus focused on the first type of neuron with place-correlated activity discovered in the hippocampus, the place cells, neurons whose firing has been reliably linked to the animals’ spatial location by many independent experiments. Thus, it could be argued that the limitations highlighted so far do not apply to the studies of hippocampal topography; place cells seem to be exceptions among neurons in high-order brain regions, and determining what they are encoding is particularly easy–or so it seems.

The discovery of place cells was one of the most fantastic findings in the recent history of neuroscience (O’Keefe and Dostrovsky 1971). These neurons that fire only when the animal is in a particular place in the environment and their receptive fields (usually called place fields) seem to form a map of the environment the animal is in (reviewed in Hartley et al. 2013). Thus, it seems logical to expect that, if there is any topographical organization of place cells, such organization would form a spatial map of the environment, with neighboring cells in the hippocampus representing neighboring places in the environment. As we discussed before, that does not seem to be the case, as no map of the environment was found, or at least not a continuous one (Eichenbaum et al. 1989; Hampson et al. 1999; Redish et al. 2001; Dombeck et al. 2010; Takahashi and Sakurai 2009; Dombeck et al. 2010; Nakamura et al. 2010). This implies that there are no topographical maps of different environments in the hippocampus. But does it mean that there is no ordered topography at all?

As we discussed before, index theory predicts the existence of an abstract topographical organization, mapping the multidimensional space of cortical locations indexed by neurons in the hippocampus. What we are going to show next is that cognitive map theory, when analyzed beyond the surface of firing correlations, predicts a very similar topography to the one proposed by index theory. The reason for this similarity in the predictions of index theory and cognitive map theory regarding hippocampal topography is that two theories propose views of neurons' receptive fields that are equivalent, isomorphic–as should be expected, as both theories deal with the same underlying system. But to see such isomorphism, we will have to take a deeper look at what is actually being encoded by place cells.

What is in a place?

The question "what do place cells encode?" seems to be a simple one: they encode the position of the animal in a given environment. But a closer look beyond the surface of firing correlations reveals a much more complicated scenario (Eichenbaum and Cohen 1988; see França and Monserrat 2018, for a detailed discussion of hippocampal representations). It is clear that place cells do not code only for the animal's relative position in the environment, as different place cells are activated when the animal occupies the same relative position in two different environments (Jeffery et al. 2003). Moreover, the activity of place cells seems to be modulated by goal-related information (Hok et al. 2007), attentional demands (Kentros et al. 2004; Fenton et al. 2010), landmarks (Geiller et al. 2017) and other sensory cues (Anderson and Jeffery 2003; Buzsáki, Battaglia 2004; Aronov et al. 2017). Even grid cells in the entorhinal cortex, believed to be the main source of inputs delivering metric information to place cells (Jeffery 2007), are modulated by sensory cues, with their pattern of activity falling apart when animals are in the dark (Chen et al. 2016) or when the geometrical shape of the environmental boundaries are changed (Krupic et al. 2015). Moreover, this dependency on environmental cues seems to be even greater in humans than in rodents (Nadasdy et al. 2017) and recent studies suggest that grid-like patterns of activity are not exclusive to spatial representations and can underlie myriad other forms of cognitive representations (Doeller et al. 2010; Constantinescu et al. 2016; Bellmund et al. 2018). Again, such modulation by sensory cues should not come as a surprise given that the entorhinal cortex integrates multimodal sensory information from the associative cortices (reviewed in Knierim 2015).

It is clear that although place cell firing is strongly correlated with the position of the animal in the environment, that is not all there is to place cells. Specifically, place cells seem to use multimodal sensory information to encode perceptual cues that define different places in any environment (Eichenbaum and Cohen 1988; Eichenbaum et al. 1989; Bush et al. 2014) and they also integrate information about the animal's goals and attentional demands (Kentros et al. 2004; Hok et al. 2007), as well as other kinds of nonspatial information (Lisman et al. 2017; Aronov et al. 2017). Thus, we could conceive the receptive field of a place cell as a region of a multidimensional space, with each dimension of this space representing a variable about which the place cell in question receives information (França and Monserrat 2018). The place cell would be responsive to a range of values of each variable about which it receives information, and the combined ranges of all variables to which the place cell responds would define the size and shape of the multidimensional receptive field. Depending on the environment the animal is in, the animal's goals and emotions, and the circumstances of the situation, only one or a few positions in the environment will contain the right combination of features corresponding to a point within the neuron's receptive field. Rapid changes in the efficiency of the synapses carrying information about that environment would ensure reactivation of the neurons in the same place (Cohen et al. 2017), creating the spatial tuning we usually observe when recording place cell activity. In other words, such abstract map of receptive fields provides all the building blocks from which representations of the environment are built (Eichenbaum and Cohen 1988; França and Monserrat 2018), those representations being much like Tolman's original proposal of cognitive maps (Tolman 1948).

It is clear that the multidimensional receptive field discussed above is far more abstract than a simple place in the environment. But such abstractedness and complexity should be expected, considering that the brain does not sense space but actually constructs it (Buzsáki and Llinás 2017). It implies that correlations found between a given stimulus and a neuron's activity may not reflect the whole picture of place cells' receptive fields fields – and some of authors of topography studies saw that clearly (Eichenbaum et al. 1989).

Note that there is an alternative way of thinking about the abstract receptive fields we proposed above. We can think of them as encoding the multimodal information they receive, or we could think of them as encoding only the location of the projections they receive. Importantly, giving that both views are based on the same thing–the neurons and their connectivity pattern–there must be possible to establish a one-to-one, topology-preserving map between the spaces of receptive fields associated with both theories. In other words, the receptive fields of hippocampal neurons proposed by the cognitive map theory and index theory are isomorphic, and so should be the topographical organization proposed by the two theories.

Topographical map of the abstract space

From the discussion above, it is clear that we should not expect a topographical map of the spatial environment in the hippocampus. If there is a topographical map, it would be more reasonable to expect it to be a map of the abstract multidimensional space that contains the receptive fields of place cells. In any given environment it should be possible to establish a mapping between this abstract space of receptive fields (either the "cognitive map" or the "index map") and a spatial representation of the environment. This mapping would be such that the different positions in the environment are all encoded in a non-topographically organized subspace of the topographically organized map of receptive fields. Such a map fits better with the observation of topographical organization in projections to the hippocampus, as it would be really astonishing if different sources of topographically organized projections carrying different modalities of information converged into a spatial map of different environments.

Experimental evidence of topographical organization in the hippocampus

At first sight, there seems to be no direct evidence in studies about the hippocampus for an abstract topographical organization of the kind discussed here. That is expected since we have been looking for the topographical map with a severely limited set of stimuli. Given that place cells should respond to a set of abstract stimuli, each with multiple variables, and that the total space of possible stimuli is certainly enormous, all three caveats for studying high-order brain regions must apply here. It may be next to impossible to choose an appropriate set of stimuli to, in a single study, determine the topographical organization of the hippocampus–or of any other high-order brain region, for that matter. This situation may give the false impression that there is no evidence for the topographical organization we have been discussing. However, this impression is wrong. The evidence is there, in the network architecture of the hippocampus.

As we mentioned before, the projections to and from the hippocampus are topographically organized. In addition, the hippocampus shows lateral inhibition, i.e., the activation of a given neuron leading to inhibition of surrounding neurons (Sloviter and Brisman 1995; Stefanelli et al. 2016). This pattern of inhibition is likely related to the fact that the majority of inhibitory interneurons in the hippocampus make local connections (Pelkey et al. 2017). In addition, at least for parvalbumin-expressing perisoma-inhibiting fast-spiking interneurons, the strength of the inhibition elicited by the interneuron decays with the physical distance between the interneuron and the principal neuron being inhibited (Strüber et al. 2015). Thus, inhibitory interneurons seem to integrate inputs from, and to inhibit, principal neurons that are physically close to them.

The overall result of this kind of organization seen in the hippocampus is a network where neighboring neurons are more likely to receive similar synaptic inputs (and thus to represent similar information) and will elicit stronger feedback inhibition in its neighbors during activity, which creates competition between neighboring neurons and prevents them from firing together–which would not make much sense if neighboring neurons did not represent adjacent stimuli, as it would be unlikely for them to be activated at the same time. As you can see, we have a topographically organized network with local competition. And what is the topographical organization about? Well, the topography will be determined by the combination of spatial distributions of all inputs to the hippocampus–an abstract topography determined by the neurons' connectivity patter (and hence their receptive fields), which when combined with reciprocal connections, indexes the brain regions that project to the hippocampus.

Additional evidence in support to the notion of an abstract topographical map comes from studies in the area of neural prosthetics. In their quest to develop the technological principles necessary for the creation of a neural prosthesis for memory enhancement/restoration, Deadwyler and collaborators (Hampson et al. 2012; Deadwyler et al. 2013) carried out two experiments that are particularly relevant to our present discussion. In both experiments, the authors used a nonlinear multiple-input/multiple-output (MIMO) mathematical model to predict CA1 firing patterns based on CA3 firing patterns simultaneously acquired through electrophysiological recording. This approach was applied to animals performing a delayed non-match to sample (DNMS) behavioral test, where animals had to memorize the position of a lever (left or right) presented during the sample phase. After an interval of variable duration, the animals had to press the lever in the opposite position relative to that presented in the sample phase. In the first study, Hampson et al. (2012) used the MIMO model to predict patterns of CA1 activity in successful trials of a given rat. Delivering those patterns of activity as electrical stimulation to the same rat in other trials enhanced the animal's performance. In other words, they extracted patterns of activity reflecting "strong codes" from when an animal gave a correct answer, fed those same patterns of activity back to the animal in other trials and that information increased the proportion of correct choices made by the animal. It is worth noting that the authors employed different controls to ensure that it was the specific pattern of activity that was enhancing performance, not, for example, the electric stimulation per se. What is more interesting, the authors also combined the predicted CA1 pattern of activity in successful trials of many different animals and created a “generalized strong code”, which was then fed back, through electrical stimulation, to different animals, also resulting in increased performance–although the increase was lesser than in the previous case, where animals received patterns CA1 activity predicted based on their own CA3 activity.

Going one step further, Deadwyler et al. (2013) performed a “memory transference” procedure, stimulating the CA1 region of naïve animals using predicted patterns of activity derived from well-trained rats. The result was an increase in the performance of the naïve rats, although performance was not as high as in trained rats–a result analogous to the findings in Hampson et al. (2012).

The experiments above imply that the activity of neurons in the same relative positions in the hippocampi of different animals represents the same information, something that should not seem very surprising, given the topographical organization of projections to and within the hippocampus (Witter 1993; Tamamaki and Nojyo 1995; Brivanlou et al. 2004). More importantly, the fact that the generalized strong code used by Hampson et al. (2012) was effective but not as much as the individual strong codes, and that the “memory transference” carried out by Deadwyler et al. (2013) was not as effective as training, is a strong evidence for the existence of topographical organization in the hippocampus. In both studies discussed above, electrophysiological recording and stimulation were carried out using electrode arrays implanted in the animals’ hippocampi. However, it is unreasonable to expect that electrode arrays were implanted in precisely the same relative positions in the hippocampi of all animals–there is certainly a small but existent margin of error there, not only due to limitations in the precision of electrode implantation, but also in part due to variations in relative positions/sizes of brain regions among animals (Galaburda et al. 1990). This means that when patterns of activity extracted from an animal are delivered to a different animal, the neurons being stimulated may not be in the exact same relative position, but will be in the same “neighborhood” (the same goes for patterns of activity generalized from multiple animals). This source of error, along with the limited number of electrodes, helps to explain the relative effectiveness of the stimulation in both studies, but the fact that those stimulation procedures improved performance, even if in a limited way, only makes sense if the hippocampus is topographically organized. If there is no topography in the hippocampus and adjacent cells do not represent adjacent stimuli, then even minor errors in the position of the electrodes would likely impair behavioral performance, not improve it. The alternative, based on studies of topography in the hippocampus, is that the authors of the studies above were so lucky that the margin of error of most of the electrodes in the array fell within the small distributed clusters of neurons with similar tuning found in some studies of topography (Eichenbaum et al. 1989; Hampson et al. 1999; Takahashi and Sakurai 2009; Nakamura et al. 2010). Suffice to say that does not seem very parsimonious.

A note on cognitive map theory and navigation

Cognitive map theory is tightly linked to spatial navigation and this function of the hippocampus is largely supported by experimental evidence (Moser et al. 2017). Importantly, we want to highlight that this view is not in contradiction with our discussion above. But to conciliate those two views we must make a distinction between what is a neuron encoding and what is that information being used for.

Let us illustrate that point with a simpler example. Take the retinal ganglion cells which respond to contrasts that are computed through neural interactions such as lateral inhibition (Meister and Tessier-Lavgine 2013). If we trace the information being received by those cells back to the relevant photoreceptors, it would be possible to represent the information encoded by the retinal ganglion cells as patterns of light spots in the bidimensional space of the field of view, and all that information, could be used to describe an abstract space with the individual receptive fields (noting that such receptive fields would also be shaped by modulatory influences, such as those of top-down processing). On the other hand, the specific patterns of light and dark that drive different cells to fire could also be represented, in an equally coherent way, as contrasts, and such interpretation is particularly useful when trying to understand further steps of visual information processing. Importantly, it should be possible to establish a topology-preserving mapping between the two representations, since both encode the same thing.

The same reasoning goes for place cells. While place cells encode abstract stimuli composed of combinations of multiple variables, the functional significance of place cell firing will depend on how this information is used by downstream regions to guide behavior (Lehky and Sejnowski 1988). We already noted before that, analogous to the case of retinal ganglion cells, it is possible to establish a mapping between the abstract space of receptive fields and the spatial representation of the environment in such a way that all positions in the environment are encoded in a subspace of the abstract space of receptive fields. It follows that some of the brain regions receiving projections from the hippocampus may use the information provided by place cells to guide spatial navigation–although precisely how this is done is an open question in the field (Moser et al. 2017). Importantly, it also follows that more information than just special position can be extracted from place cells, which is important since spatial navigation is not hippocampus' only function (Aronov et al. 2017; Tanaka et al. 2018).

Looking forward

Although the problem of characterizing the topography of higher order brain regions is extremely challenging, it is not intractable. It is important to realize that the problem of finding topographical organization in any brain region boils down to a problem of finding its neural code. The elucidation of the neural code in different brain regions is one of the main goals in neuroscience and many interesting conceptual/practical approaches were put forward in recent years aiming to improve our chances of success in this endeavor (e.g., Buzsáki 2010; Krakauer et al. 2017; Jazayeri and Afraz 2017; Panzeri et al. 2017). Of particular relevance to our problem of finding the right stimuli set is the recent movement towards a greater focus on behavior, especially the plea for the development of more complex behavioral tasks and a careful analysis of such behavioral data (Krakauer et al. 2017). Complex behavioral tasks would provide a much broader range of stimuli to the animals, which may reveal more facets of hippocampal neurons' receptive fields. The approach of providing a greater range of stimuli to investigate neural representations has already provided some stunning results for the visual cortex (de Vries et al. 2018), showing that even the receptive fields of neurons in the visual cortex are not as simple as we once thought. Thus, complex behavioral tests may help us partially circumvent one of the three caveats for studying high-order brain regions–the impossibility of presenting all possible relevant stimuli to the animal.

Another strategy that may help us in finding the hippocampal topography is expanding the search area: the EC is the main source of input to the hippocampus and we should expect some similarities in the topographical organization of EC and the hippocampus. After all, most of what we discussed about the receptive field of hippocampal place cells also applies to grid cells in the EC. Giving the topographical organization of projections between those regions, information about the organization of one them could help elucidate the organization of the other. Available evidence regarding the topographical organization of grid cells in the EC found no macroscopic topography with respect to the position of the grid vertices (grid phase) (Hafting et al. 2005), with some studies reporting that grid cells form clusters with an intra-cluster topographical organization of grid phases (Heys et al. 2014; Gu et al. 2018). However, none of those studies evaluated the modulation of grid cell firing by sensory cues or other factors. How such modulation will influence the perceived topographical organization of grid cells remains to be seen.

Interesting studies have surfaced recently regarding the information represented by grid cells in humans, which greatly expanded our conception of these representations beyond physical space (Nadasdy et al. 2017; Doeller et al. 2010; Constantinescu et al. 2016). However, although there are studies reporting sensory modulation of grid cells in rodents (Krupic et al. 2015; Chen et al. 2016), much of those findings have no clear counterpart on rodents yet. That being said, we still believe that the search for hippocampal and EC topography should focus, at least for now, on rodents, not humans. Population recording methods, such as functional magnetic resonance (fMRI), which are the only methods that can be used with human subjects, have significant limitations in their resolution (e.g., Nolan et al. 2018). Conversely, advances in our capacity to simultaneously record from large neuronal ensembles in behaving animals, coupled with the rise of more complex behavioral tests mentioned above, may give us our best shot at characterizing the topographical organization of the hippocampus and EC. Needless to say, analyzing data from large neuronal ensembles in animals performing complex behavioral tasks will bring about its own share of challenges.

Finally, it is important to report information from future studies in a way maximizes its possible use. There are countless studies already published, and many others being continually produced, that report recordings of hippocampal neurons' activity under a variety of conditions. Such studies could be used to determine the topography in the hippocampus if there was sufficient information about two aspects: first, we need detailed information on the position of the neurons being recorded (e.g., the position of the electrodes in the case of electrophysiology), so that we can make comparisons between animals; second (and this is a crucial point), we need detailed information about the behavioral tasks, as well as the animal's position, what it is seeing and how it is behaving at every moment the experiment. Although we know that this is a tall order, it is only by providing such information that the data from different studies can be combined to determine the topographical organization of receptive fields in the hippocampus. The fact is that there are only two alternatives as to how we can proceed to find the true nature of hippocampal receptive fields: we can either wait that a single study will be able to solve the matter at one take (which does not seem feasible) or we must develop new meta-analytical approaches, or adapt existing ones, to combine the data from multiple studies to estimate the multidimensional receptive fields of hippocampal neurons–which will require a lot more information from research reports than is commonly reported. It is true that the spatial resolution of the available data will nonetheless be limited by factors such as the uncertainty in the precise position of the neurons being recorded, which would hinder the resolution of the map inferred from the data. However, any rudimentary map develop this way should help us create maps of increasingly higher resolution–just as the existing information about the functional organization of the hippocampus, such as the functional specialization along the longitudinal axis (Strange et al. 2014), may help our initial attempts at developing a more fine-grained functional map.

Conclusion

Neurons in higher order brain regions can have receptive fields that are tuned to multiple dimensions, which makes it hard to describe the relation between the information each neuron receives, what that neuron computes from such information and how downstream regions use the results of such computations. Therefore, it should be no surprise that correlational methods are of limited efficiency when applied to high-order brain regions such as the hippocampus. Due to the complex nature of receptive fields in higher order regions, it becomes extremely difficult to find an appropriate set of stimuli to allow a sufficiently unbiased interpretation of statistical correlations between the presented stimuli and the neurons' firing.

Werner Heisenberg once wrote "we have to remember that what we observe is not nature herself, but nature exposed to our method of questioning" (Heisenberg 1958). That was true for physics and is certainly true for neuroscience. Neurons in high-order brain regions integrate thousands of synaptic inputs, many of those inputs providing information that is already highly processed. As such, the receptive fields of neurons in high-order brain regions can encompass a range of abstract, complex stimuli, and with our current approaches only part of that information is revealed for each stimulus set we use. Topographical organization will likely be centered not on those fractions of the receptive field, but on the whole multidimensional space. The future of the study of topography in the hippocampus and other high-order brain regions will depend on our ability to ask the right questions and look for the right answers.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

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