Grid cells require input from both place cells and head-direction cells, but not vice versa.

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Abstract

Medial entorhinal grid cells, hippocampal place cells and subicular head-direction cells together form the neural basis for a cognitive map. While increasing amounts of research has been done into these neuronal populations and their interactions with other neurons, no comprehensive overview of these interactions exists. This paper gives a coherent overview of the interactions between grid cells and place cells, and grid cells and head-direction cells. We concluded that grid cells require input from both place cells and head-direction cells for a normal function and development. Place cells do receive grid cell input, but also seem to function without it. Head-direction cells appear to have no need for grid cell information and consequently do not seem to receive it. The main arguments that led to these conclusions were based on the order of development, the effect of lesions, other signs of functional connectivity and occasionally on computation models. The recurrent connections between grid cells and place cells were hypothesised to function as an error-correction between the two neuronal populations, but further research into this hypothesis is needed. By creating a better understanding of grid cells and their interactions with other neuronal populations, this paper takes a further step towards using grid cells as a model for other higher cognitive functions of the brain.

Introduction

The way real-world location is represented in the brain has been a central question in neuroscience since the 20th century (Moser, Kropff, & Moser, 2008). Years of research have indicated that location is mainly represented in the hippocampus and the adjacent entorhinal cortex (Moser et al., 2014). Grid cells are neurons in the medial entorhinal cortex (MEC) that fire when an animal passes the space that is on any of the connecting axes of the cell's triangular grid. This firing pattern is illustrated in figure 1 (left). Grid cells rely on self-motion cues to represent location and therefore encode location in an egocentric way (Winter, Mehlman, Clark, & Taube, 2015). Each grid cell is tuned to a different grid: grids may differ in size, rotation, and position relative to the real world (Hafting, Fyhn, Molden, Moser, & Moser, 2005). Humans also possess grid cells (Doeller, Barry, & Burgess, 2010). Grid cells have anatomical connections with place cells and head-direction cells (Witter, 1993).

Place cells are neurons mainly found in CA1 and CA3 of the hippocampus that fire when an animal passes a particular space in an environment and hence, in contrast to grid cells, place cells often only have one firing field (O'Keefe & Dostrovsky, 1971). Figure 1 (middle) gives an illustration of the firing pattern of place cells. Place cells rely on environmental cues to represent location and therefore encode location in an allocentric way (Jeffery, Anderson, Hayman, & Chakraborty, 2004).

Head-direction cells are neurons that fire when the head of an animal is aimed in a specific direction, as shown in figure 1 (right) (Taube, Muller, & Ranck, 1990a). Head-direction cells are found in many brain regions, however, this paper mainly discusses the head-direction cells in the subiculum, as they are thought to be the primary head-direction cells projecting to the MEC (Winter, Clark, & Taube, 2015).

It is thought that grid cells and place cells together are able to form the most abstract representations of location the human brain possesses, in other words: they form the basis for a cognitive map (Moser et al., 2014). More specifically it is grid cell, place cell and head-direction cell information together that could contribute to updating a 'position vector' that an animal uses to know where it is and where it is heading (Sargolini et al., 2006). Even though these three neuronal populations are anatomically connected and have similar functions, little is known about the type of information that could be conveyed between these populations.
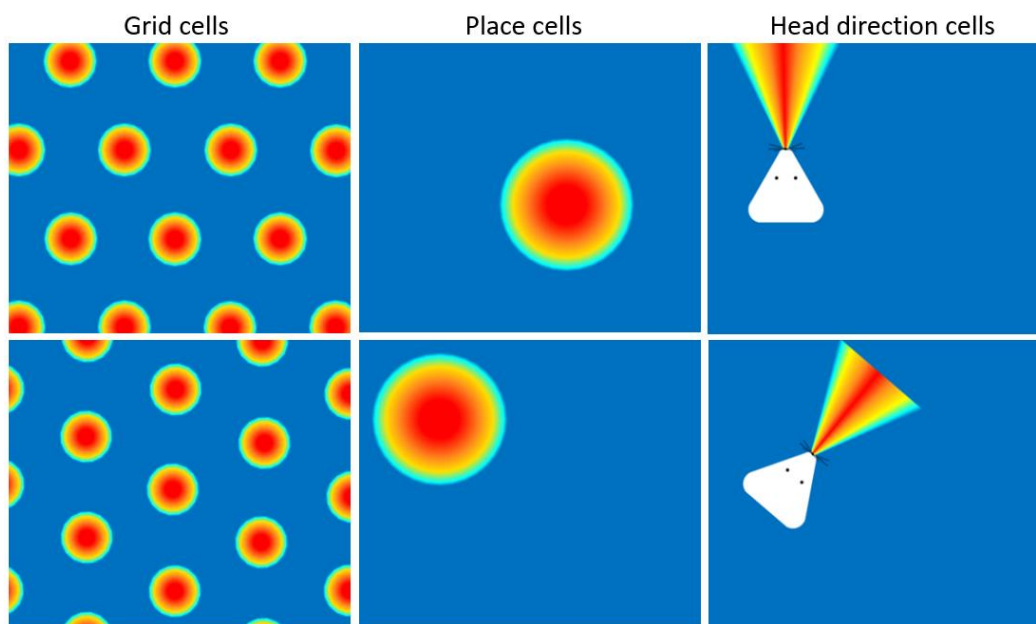

Figure 1: examples of the firing pattern of grid cells, place cells and head-direction cells. This figure illustrates the different firing patterns of each discussed cell type. The first row shows an example of a firing pattern of one cell. The second row illustrates another example of a firing pattern for a cell of the same type. The blue square indicates real space. Red indicates a high firing frequency of the neuron for that particular location, as colour fades more to blue, the firing frequency lessens.

While grid cells represent a very abstract form of information, they produce a very clear read-out: they either fire or they do not. This makes grid cells a useful model for gaining insight into other, more complex, higher cognitive functions of the brain (Moser et al., 2014).

When O'Keefe and Dostrovsky discovered place cells in 1971, they quickly saw there were many interactions with other neuronal populations, as there were cells also reacting to smells, head-direction or even possession, as well as location (O'Keefe & Dostrovsky, 1971). O'Keefe later hypothesised that a navigational system would need to be able to combine allocentric with egocentric representations of space, thus already hinting at the existence of grid cells (O'Keefe, 1976). The search for the input into place cells indeed eventually led to the discovery of grid cells by Edvar and May-Britt Moser (Fyhn, Molden, Witter, Moser, & Moser, 2004). As research has further progressed

since the discoveries of place cells and grid cells, a lot more is now known about both cell types. However, no comprehensive overview exists of their connections to other neuronal populations and the type of information that grid cells might receive from other populations. Accordingly, this paper strives to build and present such a comprehensive overview, with a focus on place cells and head-direction cells. Therefore the research questions that this paper focusses on, are: do grid cells require place cell and head-direction cell input and vice versa? And what type of information would be exchanged along these pathways? The hypothesis consists of two parts, as illustrated in figure 2:

1. Grid cells require place cell input, but place cells do not necessarily require grid cell input.
2. Grid cells also require head-direction cell input, but head-direction cells do not require grid cell input.

The interactions between grid cells and place cells will be discussed separately from the interactions between grid cells and head-direction cells.

Grid cells (MEC)

Place cells
(CA1 and CA3)
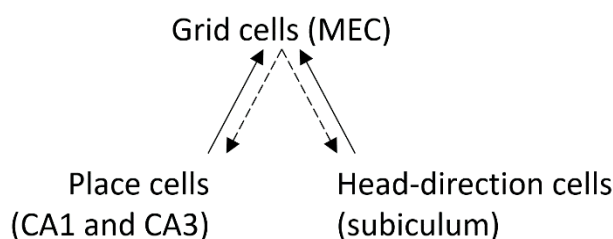
Head-direction cells
(subiculum)

Figure 2: hypotheses of this paper. This figure illustrates the expected connections between the discussed cell types. The dashed arrows indicate that the given connection might not be necessary. After each cell type the human neural location is given between parentheses.

Grid cells require place cell information, but not vice versa.

In this section we examine whether entorhinal grid cells require input from hippocampal place cells and vice versa. When the issue of the interactions between grid cells and place cells was first discussed, it was hypothesised that grid cells form the primary input source for place cells: a unique combination of active grid cells would encode for one place cell (O'Keefe & Burgess, 2005), presumably in a Fourier-like mechanism. In a Fourier mechanism multiple, different, sinusoids can be summed together to recreate a function. Depending on which sinusoids are summed together, the resulting function will change shape, as shown in figure 3. When the sinusoid with the shortest period is removed, the resulting function has a wider peak; removing the sinusoid with the longest period has the opposite, yet smaller, effect. It was however discovered that place cells reach neuronal maturity before grid cells do (Langston et al., 2010), so it seems impossible that grid cell input is necessary for place cells. This idea is further supported by Fenton et al. (2008), who discovered that place cells can fire for multiple place fields in large spaces. Therefore, the interactions between grid cells and place cells do not seem as simple as O'Keefe and Burgess originally thought.
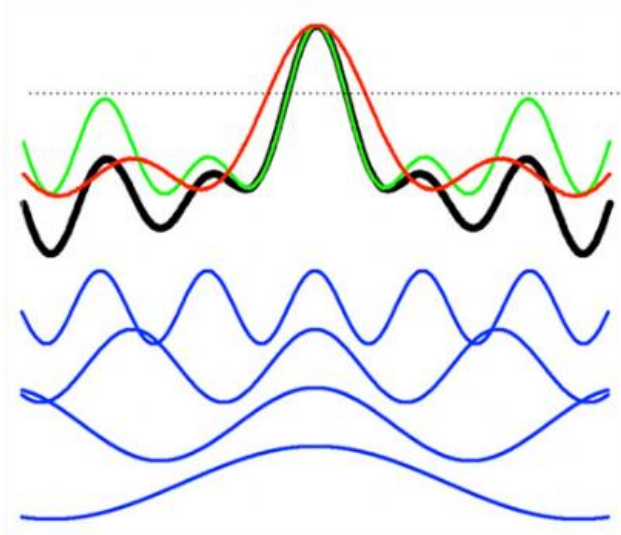
Figure 3: example of a Fourier series. *This figure shows how a Fourier-like mechanism can be used to create the contour of a one-dimensional place field. We see the black line is the product of summing four sinusoids, called Fourier components (blue). The dotted line shows the firing threshold. When the input with the shortest period is eliminated (top blue sinusoid), the place field becomes broader (red). When the input with the longest period is eliminated (bottom blue sinusoid), there is little change in the shape of the place field (green). The sinusoids in the hypothesis of O'Keefe and Burgess would be created by the grid cells, which indeed show a periodic firing frequency. Figure adapted from Kubie & Fox (2015).*

Nonetheless, it seems self-evident that the anatomical connections between grid cell and place cell networks must have a function. This idea is supported by experimental evidence: when place cells change their place field locations, called global remapping, grid cells also remap. When place cells undergo rate remapping, where only firing frequencies change without changing place field locations, grid cells do not show remapping (Fyhn, Hafting, Treves, Moser, & Moser, 2007). In addition to this, a more recent study found that lesioning the more dorsal parts of the MEC, where the grid cells with the smallest grids are located, caused an expansion of place fields in the CA1 and CA3 (this phenomenon is explained in figure 3) (Ormond & McNaughton, 2015). This supports the Fourier-hypothesis.

On the contrary, lesioning the more ventral parts of the MEC, where the larger grids lie, also caused an expansion of place fields. This contradicts the predictions of a Fourier model. Lesioning the more ventral sites, however, caused a smaller increase of place fields than lesioning the more dorsal sites. Additionally, there was a loss of Fourier components and of input from grid cells (because the MEC was lesioned), which can both create larger place fields. This means that the contraction of place fields, caused by the lesioning of the ventral MEC, might have been counteracted by the expansion caused by these two factors, resulting in a slight net expansion of place fields. Therefore, the authors concluded that the only explanation possible for their findings would be if a Fourier mechanism is indeed used to generate place fields from grid cell input. This shows that place cells definitely receive some functional input from grid cells.

Further support for this hypothesis was found when it was discovered that place cells were still active when the entorhinal cortex is lesioned, but firing rates were less stable in repeated constant conditions or after manipulations of the environment (Van Cauter, Poucet, & Save, 2008). Even stronger evidence was found later by Kanter et al. (2017): when neurons from the second layer of the MEC were depolarised, place cells in the CA1 showed significant changes in their firing pattern. These findings strongly imply that grid cell input provides place cells with a spatial reference frame.

The question now arises: is this connectivity a two-way street? Do grid cells also require place cell input? When grid cells lose the excitatory input from the hippocampus, they turn into head-

direction cells (Bonnevie et al., 2013). This shows that grid cells respond more strongly to losing place cell input, than the other way around. Moreover, this input is estimated to be crucial: a computational model made to reproduce the development of grid cells in humans shows that place cell input is crucial for a normal development of grid cells (Widloski & Fiete, 2014). This idea is supported by Langston et al. (2010), who showed grid cells develop after place cells do.

One can see there have been many articles devoted to understanding the relationship between grid cells and place cells. Some remarks must be made nonetheless: one argument in support of the idea that place cells are necessary for grid cells is based on a computational model, this model was very complete and reproduced human grid cells very well, but there is always a possibility that the model differs from the truth. The findings of the model were however supported by biological evidence, which makes the argument more plausible.

In summary, it can be concluded that place cells are essential for normal grid cell development and function. Grid cell input does not seem as essential to place cells, considering place cells develop first, although grid cells do provide place cells with a spatial reference frame.

Grid cells require head-direction input, but not vice versa.
In this section we discuss whether subicular head-direction cells and entorhinal grid cells require input from one another. Head-direction cells are neurons that, as their name implies, only fire for a specific head-direction. A true head-direction neuron therefore does not change its firing pattern when the animal moves to a different location, as long as the head is kept still. This was proven for head-direction cells in the subiculum: they indeed did not change when a rat changed location (Taube, Muller, & Ranck, 1990a). This implies that head-direction cells do not receive grid cell input, as they have no need for this spatial information.

However, when during a different experiment of Taube et al. a cue-card was moved to a different location, all head-direction cells rotated their preferred firing according to the rotation of the cue-card (Taube, Muller, & Ranck, 1990b). This implies that head-direction cells do have a preferred firing direction relative to the current environment. This type of environmental information is however not something that grid cells could provide, so this experiment implies input from a different neuronal population, possibly the place cells. In addition, the cue-card was the only stimulus in the room, therefore the rat probably perceived the entire room to be rotated. This means that, in the perception of the rat, the head-direction cells fired in the same way as before.

The article above is the only article that studied the robustness of head-direction cells for spatial information and it is fairly old. So further research is needed into the input grid cells might provide for head-direction cells. Until more is known, it seems head-direction cells have no need for grid cell input and do not even receive it.

The other way around is, in contrast, a lot more complicated. In almost all computational models attempting to explain the formation of grid patterns in grid cells it is assumed that grid cells need speed and directional information (Giocomo, Moser, & Moser, 2011). Good candidates for contributing the directional information are of course the head-direction cells, but how can we know

whether the computational models are accurate? There is experimental evidence to back this up. High concentrations of lidocaine, a drug that prevents neurons from creating an action potential, injected into the ATN (anterior thalamic nucleus), a brain area that also contains head-direction cells, caused a temporary lesion that resulted in entorhinal grid cells losing their gridlike firing pattern (Winter, Clark, & Taube, 2015). There is however one problem with this evidence: it only proves that head-direction cells located in the ATN are necessary for entorhinal grid cells. It tells us nothing about the relationship between grid cells and subicular head-direction cells.

But there is some evidence that suggests subicular head-direction cells can provide important input for entorhinal grid cells. Langston et al. (2010) found that subicular head-direction cells are fully developed when rat pups are born, while grid cells are the last to develop, of the in this paper discussed neuronal populations. Langston et al. hypothesise that this early development of subicular head-direction cells might be crucial for the development of grid cells. This early development of subicular head-direction cells also proves that these neurons do not require grid cell information for proper development, which further supports the idea that head-direction cells do not require grid cell information.

We have now seen that there definitely seems to be a necessity for grid cells to receive head-directional information. However, it is still the question whether this information originates solely in the ATN or if the subiculum is also responsible. For the question whether head-direction cells require grid cell input, the answer seems to be a clear 'no': head-direction cells fully develop before grid cells and they do not react for the type of information grid cells could provide.

Discussion

The questions discussed in this paper were: do grid cells require place cell and head-direction cell input and vice versa? And what type of information would the three cell types exchange? We discovered that both place cell and head-direction cell input is necessary for a normal functioning of grid cells. Grid cell input also seems useful for place cells, but to a lesser extent than vice versa. In contrast to this, head-direction cells don't seem to receive any grid cell information. These conclusions are depicted in the following figure:
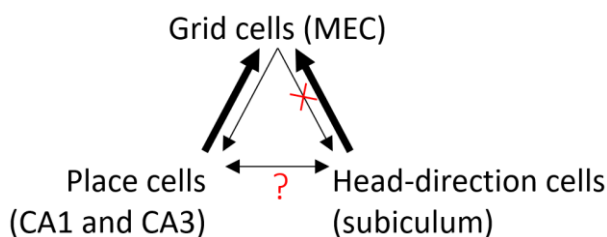

Figure 4: conclusions of this paper. *This figure is an updated version of figure 2, as shown in the introduction. It serves to quickly illustrate the conclusion this paper draws. The red cross shows which connection seems to be non-existent. The emboldened arrows show that both place cell and head-direction cell input is crucial for grid cells. The added arrow between place cells and head-direction cells is a topic not discussed fully in this paper, but is briefly discussed in the final section. The red question mark illustrates that this topic is still quite unknown.*

The conclusion we reached can be extrapolated by looking at two specific findings: (1) when grid cells are deprived of place cell input, they turn into head-direction cells, implying that this is the most important remaining input. (2) In addition, when grid cells lose input from head-direction cells they lose their characteristic firing pattern. Take these two observations together and it seems that place cells and head-direction cells together provide the most important input for grid cells. This idea of course immediately calls for further research: what would happen if entorhinal grid cells are deprived of input from both place cells and head-direction cells? By (temporally) lesioning the hippocampus, the subiculum and the ATN (to ensure grid cells receive no head-directional input), much could be learned about other input sources of grid cells.

As more is now known about the connections between the three neuronal populations, can anything be said about the type of information exchanged between grid cells and both other cell types? As mentioned in the introduction, grid cells represent location in an egocentric way, while place cells represent location in an allocentric way. The recurrent interactions between these two neuronal populations might be explained as a method for error-correction, because when one neuronal population loses their normal input, the input from the other might help retain normal function. This error-correction hypothesis could be tested further by depriving one neuronal population of their characteristic cues, and studying whether they manage to maintain a stable firing pattern when still connected to the other neuronal population.

Furthermore, as also illustrated in figure two, one interaction is yet to be discussed: how do place cells and head-direction cells interact with each other? While this subjects is not completely unknown and some research has been done (Harland et al., 2017; Knierim, Kudrimoti, & McNaughton, 1995; Yoganarasimha & Knierim, 2005), this topic also requires further research. For example, no one has yet tried to lesion the place cells, to observe what happens to head-direction cells as a result. This could be useful, since lesioning head-direction cells led to the discovery that place cells increased their place field repetition when deprived of head-directional input (Harland et al., 2017).

Additionally, a more straight-forward suggestion for further research can be found by looking at the interactions between grid cells and head-direction cells. As was mentioned in the second section, it is still the question whether the head-directional information that the grid cells receive originates solely in the ATN or if the subiculum is also responsible. We saw that lesioning the ATN resulted in a loss of gridlike firing patterns and it would be interesting to see if the same result can be obtained by lesioning the subicular head-direction cells.

Lastly, as this paper strived to present an overview of grid cells and their interactions with place cells and head-direction cells, this topic could be further explored by examining the interactions that exist with medial entorhinal speed cells, subicular boundary cells and hippocampal time cells. As these additional neuronal populations are also highly relevant spatially and are located near the three discussed neuronal populations, interactions are expected. This expectation is supported by the existence of entorhinal conjunctive cells, that fire for a combination of location, head-direction and

speed, implying that there are definitely some interactions between these neuronal populations (Sargolini et al., 2006).

This article strived to answer the question whether grid cells require input from place cells and head-direction cells, and vice versa. We concluded that grid cells require input from both place cells and head-direction cells for normal function, but vice versa this was not the case. By answering this question, a comprehensive overview was given of the information that was already available on the interactions between grid cells and other cell-types. Subsequently novel inferences were made on the basis of prior research. This paper is therefore a useful extension of earlier research. By extensively studying grid cells and their interactions, we can better understand the highly abstract representations they form. More importantly, it becomes easier to see the possible implications of grid cells as a model for higher cognitive functions.

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