Bridging the Gap Between Spatial and Mnemonic Views of the Hippocampal Formation

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Abstract

While it has long been recognized that medial temporal lobe structures are important for memory formation, studies in rodents have also identified exquisite spatial representations in these regions in the form of place cells in the hippocampus and grid cells in the entorhinal cortex. Spatial representations entail neural activity that is observed when the rat is in a given physical location, and these representations are thought to form the basis of navigation via path integration. Recent studies in nonhuman primates have suggested that similar kinds of spatial representations can be identified, even in the absence of physical movement through an environment. Here, I will highlight some recent work that addresses similarities and differences between spatial responses as identified in rodents and primates. I will also discuss areas of opportunity for future research to further our understanding of the function of the hippocampal formation.

Introduction

The ability of the mammalian brain to store and later retrieve information is remarkable. Detailed, complex memories can be formed after as little as one exposure, and those memories can be retained for decades. This ability is compromised following damage to structures located in the medial temporal lobe, including the hippocampus and surrounding cortical regions (Squire and Zola-Morgan, 1991). While it has long been recognized that these structures are important for memory (Eichenbaum et al., 1996; Jutras and Buffalo, 2010; Jutras et al., 2009; Naya and Suzuki, 2011; Rutishauser et al., 2006; Rutishauser et al., 2010; Suzuki and Eichenbaum, 2000; Suzuki et al., 1997; Wirth et al., 2003; Yanike et al., 2009), a largely parallel line of research in rodents has highlighted the contribution of these same structures to our sense of space (Doeller et al., 2010; Ekstrom et al., 2003; Fyhn et al., 2008; Hafting et al., 2005; Moser et al., 2008; O'Keefe, 1976; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978; Rolls et al., 1989; Sargolini et al., 2006). While these two perspectives on the function of the hippocampal formation, e.g., important for memory or providing an internal map, have fueled research for decades, we are still in the early stages of reconciling these two views. In that endeavor, studies with the nonhuman primate provide an important opportunity to bridge the gap between neurophysiological studies of spatial coding carried out largely in rodents and behavioral studies in human amnesic patients. In this commentary, I will discuss some recent findings from nonhuman primates that were inspired by the findings of robust spatial coding in the rodent hippocampal formation, and I will describe future areas of opportunity to advance our understanding of the hippocampal formation.

Are spatial representations in the hippocampal formation similar across species?

The existence of spatial representations in the hippocampal formation has been appreciated since the truly groundbreaking work of John O'Keefe in the early 1970's. O'Keefe and colleagues demonstrated the existence of place cells in the rodent hippocampus (O'Keefe, 1976; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). Place cells are neurons that fire action potentials whenever the rat is in a specific place in an environment, the neuron's place field. The combined activity of many of these neurons, with distinct place fields, effectively provide a map of the environment and, in more recent research, it was demonstrated that the rat's trajectory through space can be accurately decoded by measuring the activity of these neurons (Jensen and Lisman, 2000). Place cells with the sharpest and most reliable place fields are found in the dorsal part of the rodent hippocampus (McNaughton et al., 2006; O'Keefe and Nadel, 1978). In order to understand what gives rise to these spatial representations, May-Britt and Edvard Moser began recording in the dorsolateral band of the medial entorhinal cortex, the part of the rodent brain that provides the strongest input to the dorsal hippocampus. Through this work, they identified periodic spatial representations that they called entorhinal grid cells (Fyhn et al., 2004; Hafting et al., 2005). Like place cells, grid cells represent the location of the rat, but each grid cell has multiple place fields. The amazing thing about grid cells is that the multiple place fields lie in precise geometric relation to each other and form a tessellated array of equilateral triangles, a 'grid' that tiles the environment. Accordingly, a spatial autocorrelation of the grid field map produces a hexagonal structure, with 60° rotational symmetry.

While there is a large body of literature describing spatial representations in the hippocampal formation in rodents (Moser et al., 2008), relatively little is known about similar representations in the nonhuman primate (Rolls et al., 1997). One striking difference between rodents and primates is the way in which information about the external world is obtained. Rodents typically gather information by moving to visit different locations in the environment, sniffing and whisking. By contrast, primates chiefly use eye movements to visually explore an environment, and our visual system allows for inspection of the environment at a distance. Accordingly, a rodent's exploration through space may use the same neural coding mechanisms as a primate's visual exploration. Indeed, while grid cells in rodents and bats (Yartsev et al., 2011) have been identified as animals move about and explore an environment, we recently identified entorhinal grid cells in primates that represent space during visual exploration (Killian et al., 2012). As monkeys freely viewed complex natural images on a computer monitor, these cells responded whenever the monkey fixated specific regions of the monitor, independent of the stimulus content. The locations of fixation that evoked activity in an individual neuron formed the nodes of equilateral triangles that tiled the computer monitor, with hexagonal tiling in the autocorrelation. This study provided the first direct evidence for the existence of grid cells in the primate, and, importantly, suggested that grid cells may encode spatial locations even in a non-moving animal. These data are consistent with early work demonstrating hippocampal 'view cells', cells that responded whenever a monkey looked towards specific locations in the environment (Rolls, 1999). Subsequent studies investigated spatial representations in the

human hippocampal formation by recording from epilepsy patients with surgically implanted electrodes as the patients navigated through virtual environments. These studies revealed place cells in the human hippocampus (Miller et al., 2013) as well as grid cells in the human entorhinal cortex (Jacobs et al., 2013).

Other key components of the rodent hippocampal navigation system include head direction cells, cells with a heading preference when the rodent is within a particular environment (Boccara et al., 2010; Sargolini et al., 2006; Taube, 1995; Taube et al., 1990), and border or boundary vector cells, cells that are selectively active at specific distances from environmental boundaries (Lever et al., 2009; Solstad et al., 2008). In the primate, putative border cells have been identified, cells that are active whenever the monkey fixates one of the edges of the visual image (Killian et al., 2012), along with 'saccade direction' cells, cells that demonstrate selectivity for the angle of the upcoming or just-completed saccade (Killian et al., 2013). Given the potential analogy between visual exploration in primates and spatial exploration in rodents, saccade direction cells may provide directional information similar to head direction cells. The direction of saccades carries important information about past and future gaze locations. Notably, recent research in humans using virtual navigation has identified novel spatial representations, not previously identified in the rodent. In particular, neurons in the human entorhinal cortex have been identified that encode the direction of heading in a circular environment, i.e., clockwise or counter-clockwise (Jacobs et al., 2010). Taken together, these findings provide evidence that a full range of spatial representations exist in the primate hippocampal formation. Through experiments with visual exploration and virtual navigation, these studies present a new research avenue for understanding and comparing neuronal representations across species. However, they also raise important questions about the coordinate frame for these spatial representations, the extent to which these representations reflect visuospatial versus environmental navigation, and the interaction between spatial and mnemonic representations. These questions drive current and future research in this area.

Does the hippocampal formation perform similar computations across species?

The perspective that emphasizes the importance of medial temporal lobe structures to memory began in the 1950's with the report of the devastating memory impairment observed in patient H.M. following medial temporal resection to relieve otherwise intractable epilepsy (Scoville and Milner, 1957). This tradition continued through decades of research with other amnesic patients (Squire and Wixted, 2011) along with work on the nonhuman primate model of amnesia (Mishkin, 1982; Zola-Morgan et al., 1982). A fundamental understanding derived from these studies is that damage to medial temporal lobe structures produces impairment in long-term memory, but leaves short-term or working memory intact. Working memory refers to memory that is short-lasting and typically involves rehearsal; the content of working memory is information that is available to conscious awareness as long as the subject continues to rehearse it. Working memory is thought to be entirely independent of medial temporal lobe structures (Baddeley and Warrington, 1970; Drachman and Arbit, 1966; Jeneson et al., 2012; Milner, 1972; Squire et

al., 2004). In this regard, path integration provides an interesting point of comparison between the spatial and memory perspectives of the hippocampal formation. Path integration refers to the ability to keep track of one's position in space and the ability to navigate towards a reference location by way of self-motion cues. One strong hypothesis about the function of spatial representations in the hippocampal formation is that the path integrator is located *within* the entorhinal cortex (McNaughton et al., 2006). If that is true, then one would predict that damage to the entorhinal cortex would produce an impairment in path integration. However, path integration refers to an on-line computation of spatial position, and as such, falls into the realm of working memory. This hypothesis is therefore inconsistent with the distinction between short term and long term memory in terms of reliance upon medial temporal lobe structures. According to the memory tradition, in the presence of damage to the hippocampal formation, short-term memory is intact, and performance should be intact as long as information is able to be held in mind, even if that information is spatial. According to the spatial tradition, there might be an exception to this idea because the entorhinal cortex is needed for on-line computations involved in path integration.

In rodents, several studies have demonstrated impairment in path integration following lesions of the hippocampus or entorhinal cortex (Kim et al., 2013; Maaswinkel et al., 1999; Parron and Save, 2004), but see (Alyan and McNaughton, 1999). By contrast, amnesic patients with bilateral damage restricted to the hippocampus or involving the hippocampus plus adjacent cortical structures showed completely intact path integration relative to control subjects (Kim et al., 2013; Shrager et al., 2008). Notably, patients with medial temporal lobe damage performed worse when demands on long-term memory were increased by introducing distraction (Shrager et al., 2008). Together, these data suggest that in humans, the hippocampus and entorhinal cortex are not unique sites that are essential for path integration because patients perform normally as long as the route is fairly simple and can be held in working memory. It is possible that the computations needed for spatial navigation are accomplished in regions upstream from the medial temporal lobe, and that these computations arrive from cortex just as information from other modalities reaches the medial temporal lobe (Suzuki and Amaral, 1994). By this view, the critical role of the medial temporal lobe is in carrying out the operation of transforming online perceptual information into long-term memory. By contrast, rodents with damage to the hippocampal formation are impaired, even on very short paths, i.e., traveling less than 1 m and within 3 turns (Kim et al., 2013), suggesting that spatial computations that support path integration are carried out online in the hippocampal formation. There are several ways to understand these inconsistencies across species. It is possible that rodents and humans use different strategies when solving these tasks, with humans relying more on visual imagery rather than self-motion cues. It is also possible that the capacity of working memory is different for humans and rodents (Kim et al., 2013). Finally, it is possible that the hippocampal formation has evolved to perform different computations in humans from rodents. While it is currently technically challenging to perform studies of path integration in freely-moving monkeys, it is possible that future experiments combining targeted lesions in monkeys with path integration performed in virtual reality (Sherrill et al., 2013; Tcheang et al., 2011) could

advance our understanding of similarity of function between the rodent and primate hippocampal formation.

Future areas of opportunity

The demonstration of exquisite spatial representations in the form of place cells and grid cells have spawned decades of research that has advanced our understanding of the development of these representations (Langston et al., 2010; Tan et al., 2015; Wills et al., 2010) and potential mechanisms for their generation (Burgess, 2008; McNaughton et al., 2006; Welinder et al., 2008). However, what is clearly a significant gap in our understanding concerns their function. The original idea, as put forward by O'Keefe and Nadel in 1978, is that these kinds of spatial representations serve as a 'cognitive map', an internal metric for our location, derived from the integration of environmental sensory information with self-motion information. As discussed above, the idea of a 'cognitive map' leans heavily on the notion of performing spatial computations as the critical function of the hippocampus, and the idea of the entorhinal cortex as an odometer has followed from this perspective (Jeffery, 2013). In contrast, even the first report of grid cells raised the suggestion that spatial representations may provide an important substrate for memory formation:

> "… the well-established role of the hippocampus in spatial navigation may reflect the essential nature of spatial input as an element of most episodic memories rather than a specific role in computing the animal's location within a given context. Rather than calculating location per se, hippocampal networks may transform spatial and nonspatial sensory signals into distinguishable representations that can be retrieved despite noisy changes in background context."(Fyhn et al., 2004).

More recently, a specific evolutionary theory has been put forward regarding the relationship between space and memory in the hippocampal formation (Buzsaki and Moser, 2013). While spatial contextual information has always been considered a critical component of episodic memory, or memory for past events in one's life (Tulving et al., 1972), this theory suggests that spatial and mnemonic representations co-exist in medial temporal lobe structures because the mechanisms of memory evolved from mechanisms of navigation (Buzsaki and Moser, 2013). The suggestion is that travel through mental space as one recalls information and previous experiences may recruit the same neural circuitry as navigation through real space. A critical prerequisite for this idea is that spatial representations may reflect locations that the animal is holding in mind, without actually being in that location. This prerequisite has been fulfilled through recordings in the rodent hippocampus which demonstrate that ensembles of hippocampal place cells fire in sequences that can represent places in front of and behind the animal (Diba and Buzsaki, 2007), providing representations of future possible paths (Johnson and Redish, 2007; Singer et al., 2013) and behavioral trajectories towards a remembered goal (Pfeiffer and Foster, 2013). However, it is as yet unknown whether entorhinal grid cells can similarly represent positions apart from the animal's current location. Our work demonstrated that overt attention in the form of eye movements is sufficient to activate the grid cell network in monkeys (Killian et al., 2012), which suggests that grid cells may be able to support other cognitive functions besides spatial navigation. Accordingly, it is possible that spatial representations in place and grid cells may reflect the location of attention, rather than the

location of the animal (Wilming et al., 2014), and importantly, that activation of spatial representations by attention can be directed either externally, to the environment or internally, through mental travel. Further experiments with monkeys, which can be trained to attend to peripheral locations while maintaining fixation on a different location will be informative in distinguishing representations of current body position from representations of mental space.

As mentioned above, research in nonhuman primates presents an opportunity to bridge the gap between the more invasive research of cells and circuits that have been investigated in rodents and complex behaviors that can be measured in humans. In particular, I see three areas in which research in monkeys may be able to take advantage of newly available technical developments to significantly advance our understanding of hippocampal formation function. First, studies with rodents navigating virtual reality environments have identified spatial responses, similar to navigation through real space (Dombeck et al., 2010; Harvey et al., 2009). Monkeys can also be trained to navigate through virtual space via a joystick (Jutras et al., 2014), and the development of novel behavioral tasks, including tasks of spatial memory, coupled with neurophysiological recordings and eye tracking will allow for further identification of spatial representations in the primate as well as what functions these representations might serve.

Second, in order to determine the relationship between ensembles of neurons in the hippocampal formation, either with respect to modules in the entorhinal cortex or sequences of place cells in the hippocampus, one has to be able to record from large numbers of neurons simultaneously. Primate neurophysiologists have to date been limited by the size and quality of chronically implanted devices, as well as the electronics necessary to connect implanted arrays to recording hardware. More pressing, even though there are some methods available for recording from large numbers of neurons on the cortical surface, there are currently no commercially available techniques for recording from large numbers of single neurons in deep brain structures, structures that lie 3–4 cm below the dorsal surface in the monkey brain. However, developing technologies in the fabrication of multi-electrode arrays provide great promise in this regard. Fabrication techniques that involve the application of Micro-Electro-Mechanical Systems (MEMS) lithographic processes to produce dense arrays with arbitrary geometries on flexible polyimide-based films hold particular promise for recording from a large number of channels deep in the nonhuman primate brain (Lewis et al., 2014). Finally, telemetric recording systems have seen a great deal of development over the past decade, and newer systems are capable of transmitting or recording onboard wideband signal from a large number of channels (Maurer et al., 2013). Chronic arrays with hundreds of recording channels along with telemetric recordings provide the potential to examine memory consolidation by recording from the same neural ensembles during sleep and waking periods, implement full body and head movements into virtual reality settings, and even record neural activity from fully freely moving monkeys. Together, these experiments have the potential to dramatically increase our understanding of the primate hippocampal formation and the extent to which similarities of function and representation exist across species.

A Map of Cognition

Considering the reconciliation of theories regarding the spatial and mnemonic functions of the hippocampal formation, two related ideas have emerged. One idea holds that spatial representations, along with representations of time, provide the organizing structure for experience, and in that vein engender the necessary conditions for memory formation (Eichenbaum, 2014). Experiential content that is encountered close by within the structures of time or space would become associated, consistent with the idea of the hippocampal formation as being predominantly involved in relational learning, i.e., the binding or associating, of representations of multiple distinct elements into a coherent representation in memory (Cohen and Eichenbaum, 1993; O'Keefe and Nadel, 1978). A second, closely related idea is that the mechanisms of memory evolved from mechanisms of navigation in the physical world (Buzsaki and Moser, 2013). According to this idea, path integration-based mechanisms that rely on computations of self-motion relative to environmental landmarks may utilize the same mechanisms as episodic memory formation, the formation of memories that are self-referential. Engaging in mental time travel during the retrieval of episodic memories uses the same neural algorithms as navigating through space via path integration. In contrast, mechanisms that support allocentric or map-based navigation may be similar to mechanisms of semantic memory formation. According to this idea, items that have become associated through the formation of memories may lie in close proximity within some mapping of semantic relatedness. It seems that the field is converging on a reconsideration of the spatial responses in the hippocampus and entorhinal cortex as reflecting one piece of what might be called a "Map of Cognition". Rather than envisioning these neurons as providing a 'GPS' for the brain, or a map of only our spatial environment, instead these responses may be seen as contributing to a general organization of cognition. Apart from time and space, there are likely other dimensions along which cognition may be organized. Time and space present easily quantifiable continuous variables, and neural responses in the hippocampal formation have shown striking representations within these dimensions. In order to probe the extent to which neurons in the hippocampal formation may show discrete (hippocampus) or periodic/multi-bumped (entorhinal cortex) representations of cognition in general, we need to come up with clever ways to dimensionalize other aspects of the content of our experiences.

Acknowledgements

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