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Anchoring The Cognitive Map To The Visual World

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Anchoring The Cognitive Map To The Visual World

Abstract
To interact rapidly and effectively with the environment, the mammalian brain needs a representation of the spatial layout of the external world (or a “cognitive map”). A person might need to know where she is standing to find her way home, for instance, or might need to know where she is looking to reach for her out-of-sight keys. For many behaviors, however, simply possessing a map is not enough; in order for a map to be useful in a dynamic world, it must be anchored to stable environmental cues. The goal of the present research is to address this spatial anchoring problem in two different domains: navigation and vision. In the first part of the thesis, which comprises Chapters 1-3, we examine how navigators use perceptual information to re-anchor their cognitive map after becoming lost, a process known as spatial reorientation. Using a novel behavioral paradigm with rodents, in Chapter 2 we show that the cognitive map is reoriented by dissociable inputs for identifying where one is and recovering which way one is facing. The findings presented in Chapter 2 also highlight the importance of environmental boundaries, such as the walls of a room, for anchoring the cognitive map. We thus predicted that there might exist a brain region that is selectively involved in boundary perception during navigation. Accordingly, in Chapter 3, we combine transcranial magnetic stimulation and virtual-reality navigation to reveal the existence of such a boundary perception region in humans. In the second part of this thesis, Chapter 4, we explore whether the same mechanisms that support the cognitive map of navigational space also mediate a map of visual space (i.e., where one is looking). Using functional magnetic resonance imaging and eye tracking, we show that human entorhinal cortex supports a map-like representation of visual space that obeys the same principles of boundary-anchoring previously observed in rodent maps of navigational space. Together, this research elucidates how mental maps are anchored to the world, thus allowing the mammalian brain to form durable spatial representations across body and eye movements.

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ANCHORING THE COGNITIVE MAP TO THE VISUAL WORLD

Joshua B Julian

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in

Psychology

Presented to the Faculties of the University of Pennsylvania

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Dedicated to Laura
ACKNOWLEDGMENT

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ABSTRACT

ANCHORING THE COGNITIVE MAP TO THE VISUAL WORLD

Joshua B. Julian
Russell A. Epstein

To interact rapidly and effectively with the environment, the mammalian brain needs a representation of the spatial layout of the external world (or a “cognitive map”). A person might need to know where she is standing to find her way home, for instance, or might need to know where she is looking to reach for her out-of-sight keys. For many behaviors, however, simply possessing a map is not enough; in order for a map to be useful in a dynamic world, it must be anchored to stable environmental cues. The goal of the present research is to address this spatial anchoring problem in two different domains: navigation and vision. In the first part of the thesis, which comprises Chapters 1-3, we examine how navigators use perceptual information to re-anchor their cognitive map after becoming lost, a process known as spatial reorientation. Using a novel behavioral paradigm with rodents, in Chapter 2 we show that the cognitive map is reoriented by dissociable inputs for identifying where one is and recovering which way one is facing. The findings presented in Chapter 2 also highlight the importance of environmental boundaries, such as the walls of a room, for anchoring the cognitive map. We thus predicted that there might exist a brain region that is selectively involved in boundary perception during navigation. Accordingly, in Chapter 3, we combine transcranial magnetic stimulation and virtual-reality navigation to reveal the existence of such a boundary perception region in humans. In the second part of this thesis, Chapter 4, we explore whether the same mechanisms that support the cognitive map of navigational space also mediate a map of visual space (i.e., where one is looking). Using functional magnetic resonance imaging and eye tracking, we show that human entorhinal cortex supports a map-like representation of visual space that obeys the same principles of boundary-anchoring previously observed in rodent maps of navigational space.
Together, this research elucidates how mental maps are anchored to the world, thus allowing the mammalian brain to form durable spatial representations across body and eye movements.
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Edward Tolman (1948) developed the notion of cognitive maps as a heuristic for understanding the mechanisms that guide behavior. He observed that when rodents solve mazes and are faced with the opportunity to take a novel route between familiar sites, the navigator is able use the shortcut. Such behavior, Tolman argued, requires a “mental map” of navigable space that goes beyond simple stimulus-response associations. Seventy years of research have since made major advances in our understanding of the nature of the cognitive map, including the discovery of place cells in the rodent hippocampus that fire when an animal occupies particular environmental locations thus forming a “map” of navigable space (O'keefe and Nadel, 1978).

However, an underappreciated problem is that a cognitive map alone is not sufficient to guide behavior – that map must also be anchored to the external world. If you are lost in the woods with a map, for example, and have no way of determining where you are on the map, the map is useless for helping you to find your way home. Thus, cognitive mapping also requires the ability to use environmental cues to determine one’s location and orientation on the cognitive map itself. This thesis examines how the cognitive map is anchored to the external world during navigation, and whether the same principles of spatial anchoring discovered for navigation extend to other cognitive domains.

In the first part of the thesis, Chapters 1-3, I examine the cognitive and neural mechanisms involved in anchoring of the cognitive map during navigation. It is first worth noting that many navigational behaviors do not require any spatial anchoring. For example, a navigator can use internal self-motion cues (e.g., vestibular signals) to keep track of its displacement, without reference to any external perceptual information. This strategy, known as path integration, is used by many animals, including rodents, birds and insects (Mittelstaedt and Mittelstaedt, 1980; Gallistel, 1990; Etienne and Jeffery, 2004). A limitation of this strategy, however, is that error inevitably accumulates over time. When this happens, external perceptual cues must be used to recalibrate the cognitive map. Further, many species, including humans, tend not to rely
on path integration at all, and instead navigate exclusively using allothetic perceptual cues (Gallistel, 1990). Here we will consider as a case study a navigational situation in which the spatial anchoring problem is particularly acute, and one which all mobile species must be able to solve: when a navigator must to regain their bearings after becoming lost, a process known as spatial reorientation.

In Chapter 1, we review the cognitive and neural basis of spatial reorientation. One consistent theme is that the local boundaries of the environment—e.g., the walls of a room—are an extremely salient reorientation cue. Cheng (1986) first established this finding in rodents, observing that rodents primarily use the geometry of environmental boundaries to recover their orientation following disorientation, and ignore other non-boundary cues even when such cues are informative. Boundaries have since been shown to be a prepotent cue for orientation retrieval in many other species, including birds, fish, and humans (Lee and Spelke, 2010b; Cheng et al., 2013). Concordant with the importance of boundaries for reorientation behavior, place cell firing is also strongly controlled by boundaries (O'Keefe and Burgess, 1996; Keinath et al., 2017), as are the other neural components of the cognitive map, such as grid cells in the entorhinal cortex that fire in a hexagonal lattice while the animal moves along the floor (Krupic et al., 2015; Stensola et al., 2015), and border cells in the hippocampal formation that fire in proximity to boundaries at particular allocentric directions from the navigator (Solstad et al., 2008; Lever et al., 2009). Neuroimaging studies in humans have also found that neural representations of facing direction in the medial parietal cortex exhibit anchoring to boundaries during memory retrieval (Marchette et al., 2014a). Thus, extensive evidence shows that boundaries are important for anchoring the cognitive map, as reflected by navigational behavior, the neuronal coding of space, and spatial memory.

The importance of boundaries for reorientation has been historically important because it served as key evidence in an ongoing debate over the nature and modularity of the mechanisms involved in navigation (Hermer and Spelke, 1996; Cheng et al., 2013). An overlooked problem in this debate, however, is that previous studies of reorientation behavior have only focused on one
of the two core problems involved in reorientation. In particular, in order to successfully reorient, a navigator must not only retrieve their orientation (“which way am I facing?”), but must also recognize their navigational context (“where am I?”), both in specific terms (e.g., “where am I in this environment?”) and general terms (e.g., “which environment am I in?”). Most previous reorientation studies have been performed in single chamber environments in which there is no ambiguity about context identity, and so it is possible that previous reorientation studies primarily elucidated how navigators retrieve their orientation after becoming lost, without revealing how navigators solve the context recognition problem. As reviewed in Chapter 1, orientation and navigational context are represented by distinct neuronal substrates. Thus, we hypothesized that reorientation is mediated by multiple dissociable cognitive systems as well. In Chapter 2, we use an original behavioral paradigm to provide support for this idea, demonstrating that rodents recover orientation and context during reorientation through different processing streams.

In order for the cognitive map to be re-anchored to boundaries during reorientation, boundary information must first be extracted from the visual scene by the perceptual system. Surprisingly, despite extensive research showing the importance of boundaries for anchoring the cognitive map, the perceptual source of this environmental boundary information had been unexplored. In Chapter 3, we address this lacuna, by we demonstrating that the Occipital Place Area (OPA)—a scene-responsive region in the human brain near the transverse occipital sulcus—is causally and selectively involved in the use of boundaries for navigation. We speculate that perceptual boundary information extracted by the OPA serves as input to downstream regions involved in anchoring the cognitive map to the external world. This idea is described more fully in Chapter 1, in which we characterize how perceptual inputs like the OPA are integrated into the neural architecture supporting the cognitive map, thus providing a systems-level model for the mechanisms that mediate spatial anchoring.

The second part of this thesis turns to the problem of whether the spatial anchoring principles that support navigation also extend to other cognitive domains. Because the history of psychology is (in part) the history of rats learning to navigate through mazes, the cognitive map
has been largely studied in the context of spatial navigation. For example, most research on the
neural basis of the cognitive map has focused on mechanisms within the hippocampus and
associated brain areas that create geographical maps and perform navigational computations.
However, a map-like representational structure need not be limited to navigation. Indeed,
although Tolman’s experiments focused on rats solving mazes, he did not interpret his findings as
applying only to navigational computations. Rather, he employed spatial learning to model goal-
oriented decision-making, and viewed the cognitive map as a potential organizational principle for
general cognitive operations.

One non-navigational domain that might use cognitive map-like computations is vision.
Phenomenologically speaking, when we explore the environment with our eyes we have the
sense that we are looking at different locations in the world, even when we hold our head or body
fixed. Such experience suggests that, like the mental map of navigational space, visual space
might also be coded in a map-like fashion. Moreover, we experience the visual world as a
continuous unified panorama despite the fact that we move our eyes several times a second, thus
changing the image that falls on the retina. Therefore, vision also suffers from a parallel
anchoring problem to navigation.

How we experience the visual world as stable despite variability in retinal input across
eye movements has been a matter of substantial debate. It is now generally accepted that there
are two ways that the visual system might solve this problem. First, retinotopic locations could be
updated before each eye movement using information about intended eye movement direction
obtained from the motor system (Wurtz, 2008). According to this theory, there is no cognitive map
of visual space, and indeed some researchers deny the existence of any non-retinotopic visual
representation in the visual system (e.g., Gardner et al., 2008; Golomb and Kanwisher, 2011).
Second, visual space could be represented using a non-retinotopic code (e.g., Duhamel et al.,
1992; Galletti et al., 1993). Most notably, Killian and colleagues (2012) found that entorhinal
cortex grid cells in monkeys fire in hexagonal lattice of screen locations while the animals move
their eyes during free viewing of photographs. This result suggests that grid cells might support a
map of visual space in the same way as they mediate a map of navigational space. However, because animals in this study were head-fixed and there were no stimulus manipulations, it is unknown whether or not this grid representation of visual space is anchored to an external reference frame.

In Chapter 4, we demonstrate that grid-like coding of visual space is observed in the fMRI signal in human entorhinal cortex while participants move their eyes to search for a target within a visual array. This result establishes that humans represent visual space using the same mechanisms as those used to form the cognitive map during navigation. Critically, we also move beyond the Killian and colleague's (2012) results here by also showing that the orientation of the grid is anchored to the borders of the search array, adopting reliable offsets from the search display borders and rotating in concert with rotation of the search display. Thus, the visual grid code is anchored to the borders of the visual environment, paralleling properties of boundary-anchoring previously observed in rodent navigational grid cells (Savelli et al., 2008; Krupic et al., 2015; Stensola et al., 2015).

Together, this thesis addresses how the cognitive map is anchored to the visual world at multiple levels of explanation, across species and cognitive domains. The experiments presented here elucidate the systems and processes used to solve this spatial anchoring problem, thus allowing the mammalian brain to form spatial representations that are durable across body and eye movements. Ultimately, it is my hope that the work presented here offers a novel framework for understanding how the brain solves this spatial anchoring problem to guide navigation, vision, and beyond.
CHAPTER 1. The cognitive and neural basis of spatial reorientation

At some point in our lives, all of us have had the unsettling experience of losing our spatial bearings. Perhaps we came up from a subway station onto a busy street and didn't know which way we were facing. Perhaps we took a walk in the woods and lost track of where we were. In situations like these, unless another person or a navigational device such as GPS aids us, we must use information about the external world to spatially reorient ourselves. That is, we must look out at the world and use perceptual information to figure out where we are and which way we are facing. In this review, we will discuss the cognitive and neural mechanisms that underlie spatial reorientation, using data from both humans and non-human animals.

Although there is extensive work on the cognitive mechanisms mediating of reorientation, and on the neural basis of spatial navigation under oriented conditions, the neural basis of spatial reorientation surprisingly underexplored. Similarly, there has been extensive work on the visual processing of navigationally-relevant stimuli used for reorientation, such as scenes and landmarks, but less consideration as to how these stimuli are used to anchor spatial codes. Here we attempt to bridge the gap between these literatures to characterize how navigators use perceptual information to regain their bearings after they become lost.

1.1 Theoretical considerations: What is reorientation?

The experience of being lost underscores the fact that we are spatially oriented much of the time – but not always. This psychological distinction between orientation and disorientation implies the existence of an internal representation of large-scale navigable space, or cognitive map, that we use to keep track of our current spatial situation. In its strongest form, a cognitive map might be a Euclidean coordinate system (O'keefe and Nadel, 1978; Gallistel, 1990), but weaker forms of cognitive maps, such as graph-like representations (Trullier et al., 1997; Kuipers, 2000; Chrastil
and Warren, 2014), are also possible. When we are disoriented, we no longer know where we are or which way we are facing on the map, and when we are misoriented, we have plotted our map location or heading inaccurately (Weiss, 2006).

There are two ways that an oriented navigator can spatially update their coordinates on a cognitive map as they move around the world. Path integration (sometimes called dead reckoning) involves the use of idiothetic cues, such as vestibular information, proprioceptive signals, and optic flow, to actively update position and heading as one travels from a known starting position, often a home or a nest (Mittelstaedt and Mittelstaedt, 1980; Gallistel, 1990; Etienne and Jeffery, 2004). Piloting, on the other hand, involves the use of allothetic cues for updating (Gallistel, 1990). Many animals, including ants, bees, birds, and mammals use path integration, especially when foraging through unknown environments, but humans appear to rely primarily on landmark-based piloting (Epstein and Vass, 2014a). Reorientation comes into play when one’s spatial updating becomes inaccurate. It is then necessary to re-establish one’s coordinates de novo using allothetic cues. Note that reorientation is only relevant for navigators using a cognitive map-based wayfinding strategy. Navigators using more basic strategies, such as beaconing (moving directly to a goal) (Geva-Sagiv et al., 2015), view matching (moving to reduce the perceptual discrepancy between the current view and the view at the goal location) (Collett et al., 2013), or route following (a procedural strategy in which one implements a fixed series of actions in response to specific cues) (Redish, 1999), do not require reorientation, as in these cases there are no internal spatial coordinates to recover.

Reorientation can involve determination of heading direction, location, or both. In this review we will use the term reorientation as it is commonly used in the colloquial sense to encompass both functions. Formally, however, one should distinguish between heading retrieval and localization—and, as we will see, between localization in the local sense (where am I in the environment?) and the global sense (which environment am I in?). It is notable that the colloquial term seems to give a greater weight to heading retrieval (“reorient”), and indeed establishment of a correct heading appears to be the more crucial element for navigation. This may relate to the
greater consequences of an incorrect heading. If a navigator is uncertain where he is, but starts out towards his goal in the correct direction then he will get closer to his goal over time. On the other hand, if he starts out in the wrong direction, then over time his distance from the goal will increase, making this a more crucial error to avoid.

1.2 Cognitive Mechanisms of Reorientation

Psychologists and ethologists have learned much about the cognitive mechanisms underlying spatial reorientation by observing the behavior of humans and animals when they are placed in a situation where they need to recover their bearings. In this section, we describe how behavioral work has illuminated three crucial questions about spatial reorientation: (i) What are the external cues used for reorientation? (ii) What are the internal reference frames recovered? (iii) Is reorientation mediated by a single cognitive mechanism or multiple mechanisms?

What are the external cues used for reorientation?

Our surroundings provide us with myriad cues that could in principle be used for reorientation, such as nearby objects (a mailbox), distal objects (a church steeple), the spatial geometry of the environment (a T-junction), and global orientational cues (the sun). A striking aspect of reorientation behavior is that it is often most strongly influenced by local environmental geometry. This fact was first discovered by Cheng and Gallistel, who observed the behavior of misoriented (Cheng, 1986) and disoriented (Margules and Gallistel, 1988) rats as they searched for a hidden reward in a rectangular chamber (Fig. 1.1A). Although the animals would often search in the correct location, they would search almost equally often in the location that was diagonally opposite the correct one. These two locations are equivalent in terms of the geometry of the chamber as defined by the walls. The animals did not appear to use non-geometric features, such as odors, visual textures, and wall colors, for reorientation, although they could learn an association between the reward and a feature that was co-located with it. This tendency to rely on
the shape of space for reorientation has been subsequently observed in a number of species, including fish (Sovrano et al., 2002, 2003), human children (Hermer and Spelke, 1994; Hermer and Spelke, 1996), and human adults tested under conditions that place demands on language and working memory (Hermer-Vazquez et al., 1999; Ratliff and Newcombe, 2008a). Avian species and monkeys also use geometric information to reorient, though often with more equal reliance on featural information (Vallortigara et al., 1990; Kelly et al., 1998; Gouteux et al., 2001; Vallortigara et al., 2004).

Based on these results Cheng and Gallistel hypothesized that reorientation was supported by a geometric module that exclusively used the shape of surrounding space to re-establish heading after mis- or dis-orientation and was impenetrable to non-geometric featural cues. This idea has generated considerable discussion over the past 30 years. It is now clear that featural cues can have an important influence over behavior after disorientation in all species (Appendix 1.1). However, it is debated whether this is evidence for incorporation of non-geometric information into reorientation (Cheng et al., 2013), or a separate view-matching navigational mechanism in which the visual features at the target location are checked for consistency with visual memory (Lee and Spelke, 2010b). For our purposes, it is not important to resolve this dispute, but merely to note that the literature overwhelmingly has shown that environmental geometry is a powerful reorientation cue.

What aspects of spatial geometry guide reorientation? Studies of reorientation in children have addressed this question. When a rectangular enclosure was placed in the center of a cylindrical chamber, children used the shape of the enclosure to reorient not only when it was tall enough to block their view of the surroundings, but also when it was small enough to step over or even when it protruded only slightly off the ground (Lee and Spelke, 2011) (Fig. 1.1B). By contrast, children failed to reorient by the shape of a salient two-dimensional rectangular texture drawn on the floor or by the shape of an array of large, freestanding columns. When two columns were placed asymmetrically within the cylindrical room, children were found to reorient by the columns when they stood flush against the walls, forming a part of the room geometry, but not
when they were freestanding or flat textures (Lee and Spelke, 2010a) (see also Gouteux and Spelke, 2001). Reorientation thus depends specifically on the geometric analysis of three-dimensional surface boundaries. Convergent evidence for this observation comes from research in chicks, who also reorient by surface geometry, but not by two-dimensional textures on the floor or arrays of columns (Lee et al., 2012b).

A further question concerns the types of geometric information that animals extract from surface layouts. In the chambers typically used to examine reorientation, location and heading can be specified by directional relationships between walls differing either in length (e.g. a location with a shorter wall on the left) or distance (e.g. a location with a wall far from its opposite wall on the left). Studies of children in a variety of fragmented rhombic and rectangular environments provide evidence for reorientation by distance but not length (Lee et al., 2012a), though this remains a matter of some debate (Yousif and Lourenco, 2017). Another potential source of geometric information for reorientation comes from the angle at which boundaries intersect. Angular information does not appear to be a particularly powerful reorientation cue; children failed to reorient in rhombic environments in which headings and locations were differentiated on the basis of differences in angles between adjacent corners, with opposite corners sharing the same angular information (Hupbach and Nadel, 2005; see also, Lee et al., 2012a). In most environments, surfaces also differ in orientation or slope. The slope of the floor is used for reorientation in both pigeons and human adults (Nardi et al., 2010; Nardi et al., 2013), as is the slope of the ceiling in children (Hu et al., 2015). The reorientation system therefore utilizes some (direction, distance, slope) but not all (length, angle) of the geometrical properties of extended surface layouts.

There are at least three reasons why geometry may be particularly important for reorientation. First, spatial geometry is an inherently stable aspect of natural environments (the "lay of the land") (Gallistel, 1990). Indeed, there is evidence that the navigational system distinguishes between stable and unstable objects, using only the former as spatial references (Biegler and Morris, 1993). Second, boundary geometry tends to cover a large field of view and...
hence is often perceptually salient. Finally, geometry can provide strong orienting information in local reference frames. For example, Cheng & Gallistel (2005) argued that geometry is a prepotent cue because it defines the principal orientational axis of the environment, which is then used as a local orienting cue. Punctate landmarks, on the other hand, can only define a consistent direction if they are distal from the viewer. Interestingly, punctate landmarks are useful for spatial updating in oriented animals (Suzuki et al., 1980; O'Keefe and Speakman, 1987), even if they are less useful for reorientation, because the bearing between the observer and the landmark uniquely defines a direction in space if the location of the observer and the landmark are already known.

What are the internal reference frames recovered?

Location and heading—the quantities recovered during reorientation—must be defined in some reference frame. Some insight into these reference frames has come from studies using the judgment of relative direction (JRD) task (Kozlowski and Bryant, 1977). Subjects first learn an environment containing several objects. They are then removed from the environment, and asked to imagine that they are standing at one object while facing a second; they then point to a third object. To perform this task, subjects must mentally re-instantiate a location and heading on each trial—a task akin to reorientation. Because they do this in the absence of relevant perceptual cues (i.e. trials are performed outside the recalled environment), the task illuminates the internal representations used during reorientation (Burgess, 2006).

A consistent result from these experiments is that performance is orientation-dependent; that is, accuracy varies as a function of imagined facing direction. In some experiments, one imagined direction is preferred, while in others, directions opposite or orthogonal to this direction are also preferred, but to a lesser extent (McNamara, 2002). These experiments are most commonly performed using small tabletop environments, but recent work has shown that large environmental spaces are also represented in an orientation-dependent manner (Marchette et al., 2011; Frankenstein et al., 2012). For example, in one study examining JRDs defined by buildings
on a college campus with a North-South alignment, accuracy was greatest for North-facing views, and it was also greater for East, South, and West facing views than views facing diagonal directions (Marchette et al., 2011) (Fig. 1.1C). The advantage for the preferred directions appears to extend across different imagined standing positions, thus indicating that the preference is for a direction rather than for a specific view.

These results have been interpreted as evidence that we assign spatial axes to environments when we first encounter them, akin to principal axes hypothesized to support active reorientation behavior, which we then use to orient ourselves when we encounter them again, or (in this case) imagine encountering them. Spatial recall is more accurate for imagined views that are aligned with these axes than for imagined views that are misaligned. Notably, environmental geometry appears to play an important role in defining these axis (Shelton and McNamara, 2001; Mou et al., 2007), though other factors are also influential, including egocentric experience (i.e. the direction that one first enters an environment is often privileged, especially if it is aligned with local geometry) (Shelton and McNamara, 1997), the arrangement of objects within a room (Mou and McNamara, 2002), and even the intrinsic alignment of these objects (Marchette and Shelton, 2010). These results suggest that—in humans at least—these axes are established by a cognitive mechanism that is sensitive to several different possible kinds of spatial organization in the visually perceived environment. It is unclear what the equivalent mechanism would be in non-human animals, though as we will see there is evidence that they too establish orientational axes that are related to local geometry.

Is reorientation supported by a single cognitive mechanism or multiple mechanisms?
We have been discussing reorientation as a single process. However, there is some evidence that it might be divisible into separate subcomponents. Heading retrieval and localization are logically dissociable from each other: a compass indicates heading but not location, whereas a GPS system indicates location but not heading. Evidence suggests that under some circumstances animals may use different cues to solve each problem. In the Morris Water Maze,
for example, when oriented rodents are placed into a circular pool at random locations and must navigate to a hidden platform, they use distal cues provided by the surrounding experimental room (including, potentially, its shape) to determine their heading, while using proximal cues provided by distance to the wall of the pool to determine their location (Knierim and Hamilton, 2011). That is, they use the cues that are most informative to solve each component of the task. Moreover, as we will see in the next section, there is strong neural evidence for dissociation between representations of facing direction and location.

Clearer evidence for cognitive dissociation between reorientation mechanisms is presented here in Chapter 2, which focuses on the distinction between heading retrieval and context recognition. The idea is that reorientation involves not only determining one’s heading and location on a cognitive map, it also involves knowing which cognitive map to retrieve. To demonstrate dissociation between these two functions, we trained mice on a version of the Cheng and Gallistel reorientation task in which there were two rectangular chambers, each with a different reward location (Julian et al., 2015). Critically, each chamber had a distinct pattern along one wall, which was potentially informative about heading (because the location of the pattern broke the geometric symmetry of the chamber) and about contextual identity (because the patterns in each chamber were distinguishable). Strikingly, the animals used the pattern to distinguish between the chambers, but did not use it to distinguish between geometrically equivalent headings within each chamber. This demonstrates dissociation between heading retrieval and context recognition, because a treatment (i.e. the presence of the pattern) that affects context recognition has no effect on heading retrieval. Interestingly, humans show a related effect: when they navigate to remembered locations in geometrically similar rooms, they will often go to the right location in the wrong room (Marchette et al., 2017). This behavior indicates that they remember where the object is in the room (localization) without remembering which environment it is in (context retrieval). Additional evidence suggests that humans set up separate reference frames for separate navigational contexts, even when they navigate between the separate contexts, unless they are explicitly instructed to do so (Wang and Brockmole, 2003).
1.3 Neural Mechanisms for Reorientation

The preceding discussion of the cognitive mechanisms mediating reorientation provides a useful handle for linking the reorientation to the neural structures supporting the cognitive map. The neural instantiation of the cognitive map is in the hippocampus and surrounding structures (Fig. 1.2A). In the hippocampus proper, place cells fire as a function of the spatial position of the animal (O'Keefe and Dostrovsky, 1971). Different place cells prefer different locations, forming a ‘hippocampal map’ that tiles the entire navigable space and persists across visits to the same navigational context. Subsequent discoveries revealed additional components of the cognitive map navigation system, including grid cells in medial entorhinal cortex (MEC) (Hafting et al., 2005; Fyhn et al., 2007), which fire in a regular hexagonal lattice of locations, head direction (HD) cells in the postsubiculum (PoS) and Papez circuit structures, whose firing depends on the orientation of the head (Taube et al., 1990; Taube, 2007), and border cells in the MEC and subiculum, which fire when the animal is in proximity to navigational boundaries at particular allocentric directions from the navigator (Solstad et al., 2008; Lever et al., 2009). As we will see, these different components of the cognitive mapping system work together to mediate reorientation behavior.

Reorienting the cognitive map

Consistent with reorientation behavior, non-geometric features have weaker control over the orientation of the hippocampal map following disorientation. Knierim and colleagues (1995) recorded place cells in rats in a cylinder with a single proximal feature, a cue card covering 90° of the cylinder wall. Prior to testing, half of the rats were initially disoriented before being exposed to the cylinder, and the other half was oriented. Between trials the cue card was rotated to a new direction. The cue card had much weaker control over the place fields in the rats that had been disoriented during training than in the oriented rats. For the rats that were disoriented during training, place cells maintained spatially localized firing at roughly the same fixed distances from the boundary across trials, but the orientation of the entire place field map rotated at random
relative to the feature, as would be expected given the lack of polarizing geometry in a cylindrical chamber. Later studies further found that the non-geometric features can realign the place cell map under some of the same circumstances in which features guide reorientation behavior (Appendix 1.2).

Not only do features have less control over the orientation of the hippocampal map in disoriented animals, but my colleagues and I also recently found that the map is preferentially reoriented by geometry. We recorded hippocampal place cells while disoriented mice foraged in rectangular, square, and isosceles triangle shaped chambers, each containing a salient visual feature along one wall (Keinath et al., 2017). We found that the shape of the chamber solely determined the alignment of the recovered hippocampal map, even though the visual feature denoted unique orientations within the chambers that could have anchored the orientation of the hippocampal map. For example, from trial-to-trial, each place cell recorded in the rectangular chamber tended to have two place field locations, one being the 180° rotation of the other (Fig. 1.2B). Further, when mice were trained to perform the classic goal-oriented reorientation task, we found a strong correspondence between the hippocampal map alignment and the animal’s trial-by-trial behavior. Lesion studies provide concordant evidence for the importance of the hippocampus for using boundary geometry to recall previously learned spatial locations as well (McGregor et al., 2004; Vargas et al., 2004; Tommasi and Save, 2005; Horne et al., 2010b).

Notably, as with reorientation behavior, the slope of the floor also orients the hippocampal map (Jeffery et al., 2006). Thus, taken together, the hippocampal map is realigned to environmental geometry and not non-geometric features during reorientation, and this realignment mediates reorientation behavior.

The recovered orientation of the hippocampal map is likely driven by HD cell input to the hippocampal formation. The alignment of the HD cell orientation representation—the “neural compass”—is tightly coupled to the orientation of the hippocampal map (Yoganarasimha and Knierim, 2005). In the absence of reliable self-motion cues, HD cell representations of facing direction are recovered on the basis of perceptual information. This recovery of heading likely
happens rapidly: a visual cue can reset a HD cell’s preferred firing direction within 80 ms of restoring light to a room after an animal has spent a period of time locomoting in darkness (Zugaro et al., 2003). What cues recover HD cell orientation representations following disorientation? As with reorientation of the hippocampal map, features fail to reorient HD cell orientation representations in disoriented animals (Knierim et al., 1995). However, features can realign HD cell representations under some of the same circumstances in which features guide reorientation behavior and orient the hippocampal map (Appendix 1.2).

As with reorientation behavior and the place cell map, geometry also exerts greater control over HD cell orientation representations than features in disoriented animals. Knight and colleagues (2011) recorded from HD cells in an isosceles triangle shaped chamber in disoriented animals, and found that the preferred direction of HD cells rotated with rotation of the chamber geometry, despite the presence of distal features that could have oriented the map (Fig. 1.2C). HD cells in disoriented rats also shift preferred direction in conjunction with rotations of rectangular and trapezoidal shaped enclosures (Clark et al., 2012). The rotations of the HD cell preferred directions in the rectangle were more variable than in the trapezoid, consistent with the fact that rectangular chambers contain geometrically equivalent facing directions. The shape of a T-maze also exerts control over HD cell orientation (Dudchenko and Zinyuk, 2005). Dudchenko and Zinyuk (2005) monitored HD cells of rats in two rooms containing T-mazes offset relative to each other by 90 degrees. Rats were passively transported between rooms, though not explicitly disoriented. When rats were transported from one room to the other, HD cell tuning shifted in the same direction as the T-maze. Together, these results show that HD representations are recovered on the basis of environmental geometry during reorientation.

There are HD cells in a number of reciprocally connected brain structures—most notably the anterior dorsothalamic nucleus (ADN), PoS, and retrosplenial cortex (RSP)—and the preceding discussion assumed that these regions all play a similar role in reorientation (Taube, 2007). Although HD cells in each of these brain structures share a number of properties, such as tuning width, lesion work indicates that these regions serve different functions. In particular, PoS
and RSP may be more important for recovering one’s heading than ADN. ADN HD cells maintain an internally generated representation of head direction, directly integrating vestibular cues during head movement. The primary input to ADN reflects self-motion information (namely angular head velocity) from the subcortical lateral mammillary nucleus (Blair et al., 1998; Blair and Sharp, 2002). HD cells in the PoS and RSP, on the other hand, are necessary for anchoring HD representations in other regions, such as ADN, to external cues (Goodridge and Taube, 1997; Clark et al., 2010). Lesions of the RSP or PoS impair featural cue control over the ADN HD cells in oriented animals, but spare ADN HD cell directional stability when animals use only self-motion cues to update their orientation (Goodridge and Taube, 1997; Clark et al., 2010). Regions in visual cortex project to both the PoS and RSP cortex in rats (Vogt and Miller, 1983; van Groen and Michael Wyss, 1990; van Groen and Wyss, 1990), and it is likely that these projections carry the perceptual information to the HD cell circuit. Thus, an unexplored possibility is that geometry gains control of cognitive map alignment during reorientation by first orienting the HD representation in RSP or PoS. Consistent with this idea, PoS or RSP lesions or inactivation cause hippocampal place field instability in oriented animals (Cooper and Mizumori, 2001; Calton et al., 2003; Bett et al., 2013), whereas ADN lesions have much more mild effects on hippocampal spatial representations (Calton et al., 2003).

It is unlikely that the hippocampal map is reoriented by HD cell inputs directly, but rather via border cell inputs (Zhang et al., 2013). Border cells typically rotate coherently with HD cell tuning curves, suggesting that the latter could provide orientation input to border cells (Lever et al., 2009). A probable mechanistic integration of the place and HD cell systems is that HD cells provide orientation information to border cells, which in turn orients the entire place field map (Fig. 1.2D). (Grid cells likely mediate the border cell input to the hippocampal map though this remains a matter of some debate (Solstad et al., 2006; Bush et al., 2014) and moreover, given the known importance of idiothetic cues for driving grid cell firing (McNaughton et al., 2006a), it is unclear if grid cells play a direct role in the initial recovery of the cognitive map on the basis of allothetic cues.) This proposed integration of border, HD, and place cells during reorientation is consistent
with known anatomy. There are strong projections from the subiculum, including the PoS, to the MEC (Witter and Amaral, 2004), which then projects to the hippocampus (Zhang et al., 2013). The PoS likely relays heading inputs from the RSP to the hippocampus via the MEC as well (Wyass and Van Groen, 1992; Kononenko and Witter, 2012), although some direct connections between RSP and the entorhinal cortex also exist (Canto et al., 2008). An interesting implication of this idea is that if border cells receive orientation inputs from HD cells, and HD cells are anchored by geometry during reorientation, there must be an independent source of boundary geometry information to HD cells other than border cells. For example, there might exist a perceptual region that extracts boundary information from visual scenes, which then passes this information separately to HD and border cells, the latter of which are also oriented in an allocentric reference frame by HD cell inputs.

Not only do border cells likely mediate reorientation of the hippocampal map, they also play a powerful role in establishing place and grid cell location representations during oriented navigation (Muller and Kubie, 1987; O'Keefe and Burgess, 1996; Hartley et al., 2000; Burgess and Hartley, 2002; Barry and Burgess, 2007; Krupic et al., 2015; Stensola et al., 2015). For example, O'Keefe and Burgess (1996) recorded from place cells in oriented rats while systematically varying the size and shape of the environment. They found that place cells tended to respond at a fixed distances and directions from the chamber walls across these environmental deformations. Complementary results have also been found for grid cells (Barry and Burgess, 2007). Consistent with these physiological observations, neuroimaging studies have found that the human hippocampus activates proportionally with the number of spatial boundaries in an image of a scene (Bird et al., 2010), and responds strongly during learning of environmental locations with respect to boundaries (Doeller et al., 2008). By contrast, proximal features, such as objects, tend to be less important in establishing hippocampal location representations in oriented animals (Cressant et al., 1997, 1999; Doeller et al., 2008), though the precise contribution of features to the place cell location code remains a matter of debate (Knierim and Hamilton, 2011).
If border cell inputs are responsible for anchoring the place cell map to external cues that subsequently guides reorientation behavior, examination of the functional properties of border cells could elucidate the types of boundaries that guide reorientation behavior. Stewart and colleagues (2014) recorded from subicular border cells as oriented rats foraged inside in a series of circular, square, and rectangular chambers each with two major types of environmental boundaries: extended surface boundaries and vertical cliffs. Both types of boundaries present navigational interruptions to the ground plane, despite appearing quite perceptually different. The authors showed that a majority of boundary cells treated surface boundaries and vertical cliffs similarly. For instance, a cell found to respond to a boundary along a north wall fires not only to the south side of an inserted wall barrier, but also responds on the south side of a vertical cliff. The fact that boundary cells responded to vertical cliffs leads to the untested prediction that animals will use the geometry of a vertical cliff for reorientation. Conversely, reorientation behavior suggests that boundary cells will respond to a much larger range of subtle surface boundaries than those that have been examined, such as a small curb that the animal can walk over.

The importance of boundaries for establishing the hippocampal map is well characterized by the boundary-vector cell (BVC) model, according to which place cell firing fields are determined by their distance and direction to environmental boundaries (Hartley et al., 2000). The BVC model nicely compliments behavioral studies of reorientation. First, this model retrodicts that animals recover their location on the basis of boundaries at specific distances and directions from the navigator, not on the basis of location relative to boundaries of particular lengths or angles of intersection. Second, this model has been shown to predict search behavior like that observed in the standard spatial reorientation task (Barry et al., 2006). Third, border cells exhibit adult-like firing fields as soon as rats are able to freely explore their environment (at around 16-18 days old) (Bjerknes et al., 2014), and may thus provide the first critical input to hippocampal place cells, consistent with the importance of boundaries for reorientation early in development. Finally, although this model hypothesized the existence of border cells with a wide range of boundary-
distance tunings, the large majority of cells recorded thus far have firing fields close to the edges of the environment. The effect of environment size on the prepotency of geometry for reorientation might thus be due to the fact that boundaries are more proximal to the navigator in smaller environments, subsequently activating border cells which in turn lead the navigator to recover their location relative to the geometry. This hypothesis could be tested computationally by modeling search behavior in environments of various sizes with the BVC model using only border cells with short range tuning.

The cognitive atlas: neural mechanisms for context recognition

Place fields are broadly stable between visits to familiar locations. When an animal changes navigational contexts, however, a new hippocampal map is recruited in a process known as remapping (Bostock et al., 1991; Save et al., 2000). There are two major types of remapping, termed global and rate remapping. Global remapping occurs when all simultaneously recorded place cells shift to unpredictable places or stop firing altogether, quickly forming a new and distinct representation of location (Bostock et al., 1991; Save et al., 2000). Rate remapping occurs when place cells fire in the same locations relative to chamber geometry, but the firing rates reliably differ between different navigational contexts (Leutgeb et al., 2005). Remapping is thought to reflect recruitment of a different cognitive map (drawn from the cognitive atlas) corresponding to a new navigational or episodic context. As we will discuss in the next section, remapping is likely driven by contextual inputs to the hippocampal formation.

Remapping is induced by changes to a range of external sensory cues, including changes to featural cues, such as replacement of a white intramaze cue card with a black one (Bostock et al., 1991) or when a familiar testing cylinder is replaced with a novel cylinder of a different color (Kentros et al., 1998). Remapping also occurs following changes to environmental geometry, such as changing the chamber shape from a square to a circle (Muller and Kubie, 1987; Lever et al., 2002; Wills et al., 2005). The fact that remapping can be induced alterations of both featural and geometric cues is consistent with the observation that mice distinguish between
navigational contexts behaviorally on the basis of both types of cues during reorientation (Julian et al., 2015). In general, the emergence of remapping depends in part upon prior experience, and can be disrupted by inhibiting plasticity (Quirk et al., 1990; Bostock et al., 1991; Kentros et al., 1998; Lever et al., 2002). These mnemonic components indicate that remapping reflects recruitment of different maps for different contexts that goes beyond the sensory content of the environment. The occurrence of remapping may relate to those same factors that may influence whether or not a particular environment is identified as a new context during reorientation, though the precise causal relationship between remapping and context recognition is unknown.

1.4 Where do the perceptual inputs come from?

For the cognitive map to be aligned to the external world, it must interact with perceptual inputs. What are the brain regions that analyze these inputs and support the mechanisms that allow the cognitive map to be aligned? Human neuroimaging work has revealed a network of brain regions that is active during virtual or mental navigation (Ghaem et al., 1997; Maguire et al., 1997; Aguirre et al., 1998; Rosenbaum et al., 2004; Boccia et al., 2014) (Fig. 1.3A). A subset of this network is activated during viewing of navigationally-relevant stimuli such as landscapes, urban streets, and buildings, even when there is no navigational task, suggesting that they are especially important for the visual processing of navigationally-relevant information (Fig. 1.3B). These "scene regions" include the occipital place area (OPA), the retrosplenial complex (RSC), and the parahippocampal place area (PPA) (Julian et al., 2012; Malcolm et al., 2016).

**OPA: Boundary perception**

The dissociable influences of boundary and featural cues on reorientation behavior suggest that there may be dissociable regions in the visual system mediating boundary and feature perception. In Chapter 3, we provide evidence for this idea, by showing that the OPA, located near the transverse occipital and intraparietal sulci (Grill-Spector, 2003), is a key perceptual
source of boundary information during navigation (Julian et al., 2016b). Participants received transcranial magnetic stimulation (TMS) to either the right OPA or a control region before they navigated through a virtual reality arena and performed a spatial memory task that required them to learn the locations of several test objects. Critically, the locations of some of the test objects were fixed relative to the arena boundary, while the locations of others were defined relative to a proximal featural cue (landmark object). During test trials, participants were teleported into the arena and were instructed to walk to the location where they recalled a particular test object being located. Because participants started each trial in a random location and facing direction, they had to use visual information to reorient on each trial. Strikingly, TMS to OPA selectively impaired the performance accuracy for the boundary-referenced objects, but not the landmark-referenced objects. Moreover, this effect was only found when the boundary was defined by a wall, not when it was defined by a surface texture on the ground, consistent with what we would expect based on reorientation behavior. These results strongly implicate that OPA as the perceptual source of the boundary information that controls navigational behavior. A significant unanswered question is if the OPA is also the source of perceptual boundary information during a standard reorientation task.

This importance of the OPA for boundary perception dovetails with recent findings that OPA is sensitive to ‘sense’ (left vs. right) and egocentric depth information in visual scenes (Dilks et al., 2011; Persichetti and Dilks, 2016), is causally involved in discriminating scenes on the basis of their spatial layout (Dilks et al., 2013), and is involved in making spatial judgments about object locations in scenes (Nasr et al., 2013). The OPA has also recently been shown to automatically extract fine-grained information about where a navigator can move in space from visual scenes, such as whether there is a door on the left or right (Bonner and Epstein, 2017) (Fig. 1.3C). Neuroimaging studies have found a potentially homologous region to the OPA in monkeys (Nasr et al., 2011), though whether an OPA homologue exists in rodents is a critical open question. Moreover, if a rodent OPA homologue does exist, an important area of future research will be to determine whether this region is a perceptual input to entorhinal and subicular
border cells. In both humans and monkeys, the OPA shows a bias for the lower visual field, suggesting it may be particularly important for segmenting the ground plane defined relative to environmental boundaries (Silson et al., 2015; Arcaro and Livingstone, 2017).

**RSC: spatial transformations**

Perceptual information extracted by the visual system must be sent to downstream regions where it is combined with spatial information for reorientation. RSC appears to be especially important for such spatial transformations (Maguire, 2001; Byrne et al., 2007; Epstein et al., 2007b; Vann et al., 2009; Epstein and Vass, 2014a; Bicanski and Burgess, 2016). Although RSC responds when scenes are merely viewed, its response is increased when subjects use the scene to orient themselves within the larger environment—for example, when they report the direction they are facing (Epstein et al., 2007b). Activity in RSC is greater in familiar environments for which subjects have survey knowledge (Wolbers and Buchel, 2005; Epstein et al., 2007a) and shows adaptation when stimuli facing the same allocentric direction are presented sequentially (Baumann and Mattingley, 2010; Shine et al., 2016). Damage to RSC results in a deficit known as “heading disorientation” in which patients can identify places and landmarks, but cannot use them to orient themselves in space (Aguirre and D'Esposito, 1999). Recent work suggest that RSC may be divisible into a posterior portion that shows a retinotopic visual response and a more anterior portion that may be more involved in spatial memory (Silson et al., 2016). The primary locus of scene-selective response RSC is in the parietal-occipital sulcus, not retrosplenial cortex proper (Nasr et al., 2011; Silson et al., 2016), although the latter region may also play a role, possibly distinct, in re-orientation, as it shows selective response to objects that are fixed in space (Auger et al., 2012; Auger et al., 2015).

In recent studies, multivoxel pattern analysis (MVPA) of functional magnetic resonance imaging (fMRI) responses have been used to elucidate RSC’s role in spatial reorientation. In one particularly illuminating case, subjects were taught locations in a virtual environment consisting of several rectangular “museums” within a larger courtyard, and then scanned them while they
performed a JRD task on objects within the museums (Marchette et al., 2014a) (Fig. 1.3D). Participants' imagined facing direction (and, to a lesser extent, their imagined location) could be decoded from fMRI activity patterns elicited during this task. Strikingly, these spatial codes were linked to local geometry: the same patterns were elicited for geometrically equivalent directions (e.g. “facing away from the door, along the long axis of the museum”) in different museums.

These results suggest that RSC codes heading relative to the local environmental features (in this case, the walls of each museum), which is a key initial step towards solving the spatial reorientation problem. Interestingly, when subjects performed a location memory task in the same environment, they confused geometrically-equivalent locations in different museums, just as one would predict based on these RSC codes (Marchette et al., 2017). A further study on a real-world environment found that the spatial codes elicited in RSC during the JRD task are also found when subjects oriented in response to visual, rather than imagined, stimuli (Vass and Epstein, 2016).

It is unclear what is driving these RSC computations at a cellular level, although a possible candidate has emerged from neurophysiological RSP recordings in rodents. RSP contains HD direction cells that are particularly sensitive to perceptual information, as discussed, as well as direction-dependent place cells (Cho and Sharp, 2001). Interestingly, a recent report also found a population of RSP cells that have HD cell-like properties, except that these cells had head direction representations anchored to a local reference frame. Jacob and colleagues (2016) recorded RSP cells as oriented rats navigated in an environment that consisted of two connected rectangular subchambers that were polarized in opposing directions by cue cards at the end of each chamber. They observed a population of RSP neurons that fired in a specific direction in one compartment, and reversed their firing by 180° when the rat crossed into the second compartment, echoing the human fMRI results (Marchette et al., 2014). These RSP “bipolar” cells were intermixed with classical HD cells, thus providing a potential mechanism by which perceptual information could be combined with HD representations to align the HD system to the local reference frame, often defined by environmental geometry, during reorientation.
**PPA: Context recognition**

The PPA, located near the parahippocampal and lingual boundary (Aguirre et al., 1998; Epstein and Kanwisher, 1998), may be the primary neural locus of context recognition in the human brain (Epstein and Vass, 2014a). Neuroimaging studies in monkeys have observed similar scene-selective activation near the parahippocampal cortex as well (Nasr et al., 2011; Kornblith et al., 2013). Damage to the PPA caused by stroke causes profound context recognition impairments, a deficit termed “landmark agnosia” (Habib and Sirigu, 1987; Aguirre and D'Esposito, 1999; Takahashi and Kawamura, 2002). Individuals with damage to this region have relatively spared general perceptual abilities, and are able to navigate using self-motion cues or small-scale visual details (such as house number). However, these individuals tend to become lost in both familiar and novel environments because they are unable to recognize salient navigationally-relevant perceptual cues, such as buildings or landscapes, that define navigational context.

Based cytoarchitectonic characteristics and anatomical connectivity, the PPA may be homologous with rodent postrhinal (POR) cortex (Burwell and Amaral, 1998; Burwell, 2001; Furtak et al., 2007). Animal lesion studies of the posterior parahippocampal/POR region have confirmed the role of this region context recognition as well (Bussey et al., 2000; Eacott and Gaffan, 2005; Norman and Eacott, 2005; Okudzhava et al., 2009). The magnitude of navigation impairments following POR lesions is not delay dependent, confirming that, like the human PPA, the POR serves a perceptual function in rodents (Liu and Bilkey, 2002). POR is anatomically connected to the hippocampus via the MEC, thus possibly providing navigational context information to the hippocampus (Ho and Burwell, 2014). POR lesions are known to have little effect on the stability of place cell location representations over time in a single navigational context in oriented animals (Nerad et al., 2009), but a critical open question is whether POR damage results in impairment of hippocampal remapping across contexts during reorientation.

Recent studies examining the PPA’s pattern of fMRI response provide convergent evidence for the importance of this region in context recognition. The PPA response pattern is similar for scenes depicting the inside and outside of the same navigational context (buildings),
irrespective of task, but only in participants that have learned the association between the inside and outside of those buildings through navigational experience (Marchette et al., 2015b) (Fig. 1.3E). The pattern of response in the PPA is also directly related to scene recognition behavior; when scenes are presented very briefly and masked to make recognition difficult, the categories confused by subjects are the same as those represented similarly by the PPA (Walther et al., 2009; Walther et al., 2011). PPA scene-specific responses occur at short latencies after stimulus onset (Bastin et al., 2013), suggesting that it may reflect bottom-up processing of cues useful of identifying navigational context.

The PPA is sensitive to the presence of boundaries in scenes that form a navigable space (Epstein and Kanwisher, 1998; Commiteri et al., 2004; Kamps et al., 2016) and represents the shape of the space defined by boundaries (Kravitz et al., 2011a; Park et al., 2011; Harel et al., 2013). The PPA is also sensitive to features that could serve as useful indicators of context, such as texture and material properties of objects (Cant and Goodale, 2007) and visual summary statistics of object ensembles (Cant and Xu, 2012). Further, the PPA responds strongly when participants view images of objects that have properties that would make them landmarks as well (Troiani et al., 2012), such as if they are large and stable (Konkle and Oliva, 2012; Julian et al., 2016a), distal (Amit et al., 2012), strongly associated with particular navigational contexts (Bar et al., 2008), or have been previously encountered at navigational decision points (Janzen and van Turennout, 2004; Schinazi and Epstein, 2010a). Together, these results are consistent with the idea that the PPA is involved in context recognition on the basis of both boundary and featural cues. An alternative possibility is that the PPA is involved in identifying landmarks, not for the purpose of context recognition, but rather for identifying useful orientational cues. However, this account is unlikely for two reasons. First, the PPA is insensitive to ‘sense’ (left-right) information in scenes, which would be necessary if this region were to be involved in computations relating to the orientation conveyed by landmarks (Dilks et al., 2011). Second, POR lesions in rodents do not disrupt featural control over HD cell orientation representations, despite impairing context recognition (Peck and Taube, 2017).
Network architecture of the perceptual inputs to the cognitive map

To characterize the network architecture of the perceptual inputs to the hippocampal formation in humans, we performed a functional connectivity analysis using resting-state fMRI data from a large cohort of participants (see Appendix 2 for full methods and results). We found evidence for two pathways from anatomical regions overlapping OPA to the hippocampus, one dorsal stream pathway through the superior parietal lobule and anatomical regions overlapping the RSC, and another ventral stream pathway through anatomical regions overlapping the PPA (Fig. 1.4). This finding is consistent with anatomical and functional connectivity studies in monkeys, which also reveal separate dorsal and ventral stream pathways from anatomical regions overlapping the OPA to the hippocampus (Kravitz et al., 2011b). These results suggest that the OPA sends perceptual boundary information to the RSC via a dorsal stream pathway, which integrates this perceptual information with spatial representations in a local reference frame. At the same time, the OPA serves as an independent input to the PPA via a ventral stream pathway, which incorporates this perceptual boundary information into its context recognition computation. We propose that the RSC and PPA thus serve as separate inputs to the hippocampal formation for re-anchoring the cognitive map during reorientation.

1.5 Conclusions

All mobile organisms need the ability to use perceptual information to recover their bearings after becoming lost. This review provides support for a tentative sketch of the cognitive and neurobiological basis of reorientation behavior. When a lost navigator must recover her bearings, boundary information is first extracted from visual scenes by the OPA and sent via separate pathways to the context recognition and heading retrieval systems. The navigational context in which she is located is identified by the context recognition system (PPA / POR), on the basis of both boundary and featural information. The heading retrieval system (RSC/RSP and PoS) rapidly retrieves facing direction in a local frame of reference relative to the stable environmental
cues, typically environmental geometry represented in terms of distance and direction between boundaries. The hippocampal instantiation of the cognitive map is then recovered via border cell inputs, which are oriented the right way around by boundary-anchored HD cell inputs. This recovered cognitive map, re-anchored to perceptual cues in the external world, then guides goal-directed behavior. This network description of the neural basis of reorientation offers a novel framework for understanding how the cognitive map is recovered after a navigator becomes lost. Reorientation has historically been discussed as a monolithic navigation process carried out by a single "reorientation system" (Wang and Spelke, 2002; Lee and Spelke, 2010b; Twyman and Newcombe; Landau and Hoffman, 2012). But the preceding review demonstrates that reorientation is supported by multiple interacting systems that must work in concert for a lost navigator to get on her way.
Figure 1.1. Cognitive mechanisms involved in reorientation. A) In the standard reorientation task, a disoriented navigator is trained to locate a reward in one corner (C—correct corner) of a small rectangular chamber with polarizing features along the walls (e.g., black stripes). Navigators are typically found to use boundary geometry to reorient, searching equally often at the correct and geometrically equivalent opposite (G) corners, and to ignore the non-geometric features, even though they are informative. B) Subtle surface boundaries are used for reorientation, such as a small curb (cues used: top row) or sloping edges (cues used: bottom row), but a salient marking on the floor (cues not used: top row) or an array of unconnected pillars (cues not used: bottom row) are ignored (reproduced from Lee and Spelke, 2011). C) Spatial memory is orientation dependent. Using a JRD task, memory for the relative locations of buildings on a college campus (map shown on left) was found to be better when imagined facing was aligned to the cardinal directions than misaligned (reproduced from Marchette, et al., 2011). There was also an overall effect of better memory when participants imagined facing North. For this college campus, the geometric layout of the buildings is also aligned to the cardinal global directions.
Figure 1.2. Neural mechanisms involved in reorientation. A) The neural instantiation of the
cognitive map is supported by four primary cell classes: place, grid, head direction (HD), and
border cells. An example firing field for each cell class is shown. B) Following disorientation, the
hippocampal map is anchored by boundary geometry, and not polarizing non-geometric features.
For this example place cell, from trial-to-trial, two place fields were observed relative to chamber
geometry, one being 180 degree rotation of the other (example cell adapted from Keinath et al,
2017). C) As with the place cell map, HD cell orientation representations are also anchored by
geometry from trial-to-trial following disorientation. Disoriented animals navigated in an isosceles
triangular shaped chamber (the black lines show the path of the animal). The red arrow denotes
the preferred firing direction of an example HD cell across trials (example cell adapted from
Knight et al., 2011). D) Proposed network architecture for anchoring the cognitive map to
boundary geometry during the standard reorientation task in a single navigational context.
Schematic of the scene viewed by the navigator during the task is shown to the right of “Allothetic
cues”.
Figure 1.3. Perceptual inputs to the cognitive map. A) Meta-analysis of human brain regions activated during navigation shown on the inflated cortical surface. Neurosynth was used to perform an automated meta-analysis of 64 studies of navigation (www.neurosynth.org; (Yarkoni et al., 2011)), revealing common activation across these studies in parahippocampal cortex, retrosplenial cortex, entorhinal cortex, superior lateral occipital and posterior parietal areas, as well as the hippocampus (Map thresholded at \( p<0.01, \text{FDR-corrected} \)). Only the right hemisphere is shown, though similar brain regions are also observed in the left hemisphere. B) Perceptual inputs to the cognitive map include three regions (OPA, RSC, OPA) that respond more strongly to scenes than other visual stimuli, defined here in a large group (\( n=42 \)) of participants using standard methods (Julian et al., 2012). C) The similarity of the OPA response pattern reflects the locations of fine-grained navigational affordances in scenes (i.e., the position of doorways), irrespective of other perceptual details present in the scene (e.g., paintings) (adapted from Bonner et al., 2017). Example stimuli shown on left; EVC corresponds to early visual cortex. D) RSC represents heading in a local reference frame during a JRD task (adapted from Marchette et al., 2014). During training, participants learned the locations of objects (denoted by circles) inside virtual reality museums. On each JRD trial during scanning, participants imagined facing each
object encountered during training in two museums. The RSC response pattern was similar for facing directions across museums defined in a local, but not global, reference frame. E) PPA shows a similar pattern of response to images of scenes depicting the inside and outside of the same buildings, but only in participants who had navigational experience with the buildings (University of Pennsylvania – Penn students), not in participants who did not (Temple students) (adapted from Marchette et al., 2015). Example stimuli are shown on the left; Error bars denote ±s.e.m., ** p<0.01, **** p<0.0001
Figure 1.4. Network architecture of the perceptual inputs to the hippocampus. Resting-state functional connectivity analyses (see Appendix A1.2 for details) reveal two separate pathways by which perceptual boundary information represented in the OPA could be sent to the hippocampus (HIPP) to re-anchor the cognitive map during reorientation: one ventral stream pathway shown in red through medial temporal lobe areas (lingual gyrus, parahippocampal cortex, and fusiform cortex) overlapping with the PPA, and one dorsal stream pathway shown in blue through medial parietal regions (posterior cingulate and precuneus) near the RSC via posterior parietal regions (superior parietal lobule).
CHAPTER 2: Context recognition and heading retrieval are mediated by dissociable cognitive systems in mice


2.1 Abstract

A lost navigator must identify its current location and recover its facing direction in order to restore its bearings. We tested the idea that these two tasks—context recognition and heading retrieval—might be mediated by distinct cognitive systems in mice. Previous work has shown that numerous species, including young children and rodents, use the geometric shape of local space to regain their sense of direction after disorientation, often ignoring non-geometric cues even when they are informative. Notably, these experiments have almost always been performed in single-chamber environments in which there is no ambiguity about context identity. We examined the navigational behavior of mice in a novel two-chamber paradigm in which animals had to both recognize the chamber in which they were located (context recognition) and recover their facing direction within that chamber (heading retrieval). In two experiments, we found that mice used non-geometric features for context recognition, but simultaneously failed to use these very same features for heading retrieval, instead relying exclusively on spatial geometry. These results suggest the existence of separate systems for context recognition and heading retrieval in mice that are differentially sensitive to geometric and non-geometric cues. We speculate that a similar cognitive architecture may underlie human navigational behavior.
2.2 Introduction

A navigator who becomes lost must solve two tasks in order to regain her bearings. First, she must identify her current location, a process we term context recognition. Second, she must identify her current facing direction, a process we term heading retrieval. These two tasks are logically dissociable from each other: a “you are here” map identifies location without revealing heading, whereas a compass reveals heading without identifying location. Neurophysiological work on rodents suggests that the outputs of these two processes are represented by distinct neural populations: location is coded in the hippocampus, in both general terms (different environments elicit different hippocampal maps) and specific terms (place cells fire at specific coordinates within an environment), while heading is encoded by head direction (HD) cells in several structures including the postsubiculum, thalamus, and retrosplenic cortex (O'Keefe and Dostrovsky, 1971; Taube, 2007; Colgin et al., 2008). However, little is known about the systems that determine these quantities from perceptual inputs. In particular, it is not known whether context recognition and heading retrieval are mediated by the same or different processing streams.

Here we use a novel behavioral paradigm to test the hypothesis that the mechanisms that mediate context recognition at the coarse level (i.e., identification of the current environment) in mice are dissociable from the mechanisms that mediate heading retrieval. We employ a variant of a spatial reorientation paradigm that has been used extensively to study navigation behavior in a variety of species, including rodents and human children (Cheng, 1986; Gallistel, 1990; Hermer and Spelke, 1994; Cheng et al., 2013). In the standard version of the paradigm, the animal (or human) navigator is first familiarized with a rectangular chamber with a hidden reward in one of the corners. Once it learns the location of the reward, the navigator is then removed from the chamber, disoriented, and placed back into the center of the chamber facing a randomly chosen direction. By observing which corner the navigator chooses when searching for the reward, it is possible to determine which cues it uses to orient itself in space. Many studies using this paradigm have demonstrated that geometric cues (i.e., the shape of the chamber) exert strong
control over behavior in this task, often to the exclusion of other cues. For example, when rats see food buried in a rectangular chamber and are then disoriented, they search equally often in the correct corner and in the corner that is diagonally opposite. This indicates that the animal is using geometry as a cue, as these two corners have the same spatial relationship to the chamber geometry. The animals will often ignore other orienting cues such as odors, visual patterns, and wall color, even when these cues provide polarizing information that could potentially resolve the geometric ambiguity (Cheng, 1986; Margules and Gallistel, 1988). Although the exclusive reliance on geometric cues is not found under all circumstances (Learmonth et al., 2002; Cheng and Newcombe, 2005), it has been observed in a large number of studies.

An important aspect of this classical paradigm, which to our knowledge has not been previously commented upon, is the fact that there is no ambiguity about the identity of the environment, as the experiment is typically performed within a single chamber (although see (Graham et al., 2006; Horne et al., 2010a)). Thus, in the standard version of the task, the navigator needs only to reestablish his or her heading direction. Therefore, to examine context recognition and heading retrieval simultaneously, we used a novel version of the task in which there were two chambers, each with unique identifiable features and a different reward location. We first taught the mice the locations of the rewards in each chamber, and then tested them while alternating between the two chambers on different test trials. To find the reward in this case, the mouse must both identify the chamber and determine which direction it is facing within the chamber—in other words, it must perform both context recognition and heading retrieval.

We hypothesized that these two processes—context recognition and heading retrieval—would be differentially controlled by geometric and non-geometric cues. To test this hypothesis, we used geometrically identical rectangular chambers that contained unique features that allowed them to be discriminated. In Experiment 1, each chamber contained a striped feature attached to the short wall, which was vertically aligned in one chamber but horizontally aligned in the other. In Experiment 2, each chamber contained a vertically striped feature, which was attached to the short wall in one chamber but attached to the long wall in the other. Critically, in both cases, the
feature was potentially informative about both the identity of the chamber and heading within the chamber. To anticipate, we found that mice used the features to disambiguate the chambers but not to disambiguate headings within the chambers. In other words, they used features for context recognition but not heading retrieval, thus demonstrating a dissociation between these two processes.

2.3 Results

We first set out to show that mice trained in a classical single-chamber reorientation paradigm use geometric cues to reorient themselves while ignoring non-geometric cues—a pattern often found in other species. Previous work has demonstrated that mice use geometry for reorientation but the effect of polarizing non-geometric cues in the presence of orienting geometry has not been tested (Twyman et al., 2009). We trained 16 disoriented mice to locate a reward in the corner of single rectangular (20 x 30 x 25 cm) chamber with a polarizing cue along one short wall (Fig. 2.1A). Figure 2.1B presents the average proportion of trials that mice searched in each of the four chamber corners over 16 total test trials. Mice searched for the reward more often in the two corners that were geometrically appropriate (C and R in Fig. 2.1A) than in the two corners that were geometrically inappropriate (F and N), replicating the previous finding of sensitivity to geometry (Cohen’s $d = 1.30$, $t(15) = 5.20$, $p < 0.001$). Moreover, they failed to use the orienting feature to distinguish the correct corner (C) from the geometrically equivalent corner that was diagonally opposite (R), thus showing the same insensitivity to non-geometric cues when determining facing direction often found in other species (Cohen’s $d = 0.39$, $t(15) = 1.57$, $p = 0.14$).

We then examined the navigational behavior of 16 disoriented mice in a novel two-chamber paradigm. The animals were presented alternately with two rectangular chambers that were geometrically identical (20 x 30 x 25 cm) but distinguishable by stripes along one short wall. The stripes were vertical in one chamber and horizontal in the other (Fig. 2.2A). Because this
feature both differentiated between the chambers and acted as a polarizing cue, it could be used for both context recognition and heading retrieval. In one chamber, mice were rewarded when they searched in the left corner nearest the striped wall, and in the other, when they searched in the right corner nearest the striped wall. We predicted that mice would use the stripes to identify the chamber in which they were located, but would not use the stripes to disambiguate between geometrically equivalent headings.

The results upheld our predictions. Figure 2.2B presents the average proportion of trials that mice searched in each of the four corners in each of the two chambers (16 total test trials per chamber). In neither chamber did the distribution of search frequencies across all corners (C, R, N, and F in Fig. 2.2A) differ significantly from those of the control animals trained in the classical single-chamber paradigm (both $\chi^2(3)$’s < 6.05, $p$’s > 0.11). In both chambers, the animals searched more often in the geometrically appropriate corners (C and R in Fig. 2.2A; Bolded in Fig. 2.2B) than the geometrically inappropriate corners (N and F in Fig. 2.2A) (horizontally-striped chamber: Cohen’s $d = 0.65$, $t(15) = 2.59$, $p = 0.02$; vertically-striped chamber: Cohen’s $d = 0.68$, $t(15) = 2.73$, $p = 0.02$; Fig. 2.2C). This observation was confirmed by a 2 (absolute corner location: long wall left or right) x 2 (chamber: vertically-striped or horizontally-striped) repeated-measures ANOVA, which revealed a significant interaction between absolute corner location and chamber ($F(1,15) = 22.72$, $p < 0.001$, $\eta_p^2 = 0.60$; Fig. 2.2C). Because the geometrically appropriate corners differed between the two chambers, this pattern of performance indicates that the mice must have distinguished between the chambers. Given that the identity of the feature (horizontal vs. vertical) was the only thing that differed between the two chambers, these findings strongly suggest that the animals used the feature for chamber discrimination (i.e., context recognition).

We then performed an additional statistical test to see if the animals used this feature to distinguish between geometrically equivalent headings within each chamber. The classic finding with rectangular chambers is that animals do not distinguish the rewarded location from the diagonally opposite location, even in the presence of a non-geometric polarizing cue. We
replicate the classic finding here: in neither context did animals search more at the correct location than the diagonally opposite corner (both Cohen’s d’s < 0.14, t(15)’s < 0.57, p’s > 0.58). Thus, the mice used the striped feature to distinguish between the chambers, but simultaneously failed to use this potentially informative feature to disambiguate between headings. That is, for heading retrieval, the mice solely relied on geometry.

In Experiment 2, we further explored the range of features that are used for context recognition. In particular, we asked whether the mice could discriminate between the chambers based on the spatial location of a feature relative to chamber geometry. The paradigm was similar to Exp. 1. A new group of disoriented mice (n=16) were trained to locate rewards in the corners of two rectangular chambers, with different reward locations in each chamber. In this case, the same vertical striped feature was present in both environments, but in different locations: in one chamber the feature was on a short wall, while in the other chamber it was in the center of a long wall (Fig. 2.3A). Thus, to disambiguate the chambers, the animals had to process the location of the feature relative to the chamber geometry. They could not distinguish the chambers on the basis of feature identity alone.

Figure 2.3B shows the average proportion that mice searched in each of the four corners, separately for each context. In neither chamber did the distribution of search frequencies across all corners differ significantly from those of the control animals trained to locate a reward in the classical single-chamber paradigm (both $X^2(3)$’s < 2.61, p’s > 0.46). We again found that in both chambers mice searched more often in the geometrically appropriate corners than in the geometrically inappropriate corners (long-wall chamber: Cohen’s d = 1.31, t(15) = 5.58, p < 0.0001; short-wall chamber: Cohen’s d = 0.92 , t(15) = 3.93, p = 0.001; Fig. 2.3C). Confirming this, a 2 (absolute corner location: long wall left or right) x 2 (chamber: long wall feature or short wall feature) repeated-measures ANOVA revealed a significant interaction between absolute corner location and chamber ($F(1,15) = 54.578$, $p < 0.001$, $\eta_p^2 = 0.78$; Fig. 2.3C). Moreover, we once again observed that animals searched in the correct corner and the geometrically equivalent corner with equal frequency (both Cohen’s d < 0.39, t(15)’s < 1.59, p’s > 0.14).
These results replicate the pattern of findings from Experiment 1. Once again, mice used a cue to distinguish between the chambers and then ignored the very same cue when determining their facing direction. In this case, the cue in question was the location of the striped feature relative to the geometry. These results suggest that the context recognition system can utilize a variety of cues, including both spatial and non-spatial features, and that information about the location of a cue relative to chamber geometry can be incorporated into its calculations. The heading retrieval system, on the other hand, seems to rely solely on geometry (at least in our experiments; see 2.4 Discussion).

A possible alternative account of the results in Exp. 2 is that the animals did not, in fact, distinguish between the chambers, but rather treated the two contexts as identical and used the feature to specify a principal orientational axis for the environment (Cheng and Gallistel, 2005). We think such an account is unlikely, as it would require the animals to ignore the geometry of the room when determining heading; moreover, it would require them to use the feature as an axis-defining cue (North-South vs. East-West) but not as a polarizing cue (North vs. South).

Nevertheless, to test this possibility, we ran 15 of the 16 animals in Exp. 2 in two square chambers (one large and one small) following the last day of testing. Each of these chambers had the vertical striped feature along one wall (Fig. 2.4). We reasoned that if mice were using the feature to define the principal axis while ignoring geometry, then they should continue to use this strategy in the square chamber. In this case, they should search in the location on the left side of the feature and also in the diagonally opposite corner. However, this is not what we observed. Instead, the mice searched no more often at left-of-feature corner and the corner diagonally opposite than they did at right-of-feature corner and the corner diagonally opposite (small-square chamber: Cohen’s $d = 0$, $t(14) = 0.00$, $p = 1.0$; large-square chamber: Cohen’s $d = 0.23$, $t(14) = 0.90$, $p = 0.38$; Fig. 2.4). Thus, the mice did not use strategy of going to the corners on the left-of-feature diagonal during the main part of Experiment 2, but rather used the location of the feature to distinguish the chambers and the geometry of the chamber to determine their heading.
Taken together, the results from Experiments 1 and 2 indicate that when disoriented mice were faced with a situation in which they had to both identify their environment and also re-establish a sense of direction within that environment, they used both non-geometric (Exp. 1) and geometric (Exp. 2) information to identify their environment, but only geometric information to re-establish their sense of direction. To further test this account, we calculated the Bayes factor (Gallistel, 2009; Dienes, 2011) comparing the alternative hypothesis that the geometrically appropriate corners were chosen more often than the inappropriate corners to the null hypothesis that the geometrically appropriate and inappropriate corners were chosen equally often. Combining data from both experiments, this analysis revealed an average Bayes factor of 3.81 in favor of the alternative hypothesis that animals used the feature to discriminate chambers, a magnitude that is considered to provide “substantial” evidence (Jeffreys, 1998). To verify that the same cues that were used for context recognition were ignored for heading retrieval, we computed the Bayes factor comparing the alternative hypothesis that animals searched more at the correct corner than the diagonally opposite corner to the null hypothesis that the proportion of searches at both geometrically appropriate corners were equal. In this case, the average Bayes factor was $1.79 \times 10^{-6}$, which provides evidence in favor of the null hypothesis.

2.4 Discussion

Using a two-chamber spatial reorientation paradigm, we found a dissociation between two fundamental components of spatial navigation: context recognition and heading retrieval. When disoriented mice were faced with a situation in which they had to both identify their environment and also re-establish a sense of direction within that environment, they used both geometric and non-geometric information to identify their environment, but relied solely on spatial geometry to retrieve their heading. Critically, the very same cue that was used for context recognition was ignored for heading retrieval, even though it was highly informative in both cases. Thus, our results cannot be explained by unequal salience of cues.
We demonstrated this dissociation between context recognition and heading retrieval in two experiments. In Experiment 1, the animals searched for hidden rewards in two geometrically identical rectangular chambers, each of which had a distinguishing feature (horizontal vs. vertical stripes) along one of the short walls. In Experiment 2, the chambers were also geometrically identical rectangles, but in this case the distinguishing feature was the location of a vertically striped feature relative to the chamber geometry (along short wall vs. along long wall). In both experiments, we reprised the classic results from the literature by showing that the animals searched for the reward more often in the two corners that were geometrically appropriate for each chamber than in the corners that were geometrically inappropriate; furthermore, they did not distinguish between the two geometrically appropriate corners (i.e., the correct corner and its rotational opposite). The fact that the animals chose the corners that were geometrically appropriate for each chamber indicates that they must have used the identity (Exp. 1) or location (Exp. 2) of the striped feature to distinguish between the chambers, as these were the only disambiguating cues. However, the fact that they did not distinguish between the two geometrically appropriate corners indicates that they did not use the striped features to distinguish between headings, although these features clearly polarized the environment. These results demonstrate a functional dissociation between context recognition and heading retrieval: the striped feature acts as a treatment that selectively affects one process (context recognition) but does not affect the other (heading retrieval). (See Appendix 3.1 for further consideration of this point.)

To our knowledge, this is the first demonstration of this dissociation. A previous reorientation study by Horne and colleagues reported that rats could discriminate between a rectangular chamber with all black walls and a rectangular chamber with all white walls (Horne et al., 2010a). This result is consistent with ours insofar as it indicates that the animals can use non-geometric cues for context recognition. However, because the wall colors in the Horne study did not specify a unique heading within the chambers, their design did not allow them to dissociate between context recognition and heading retrieval as we do here.
Why might heading retrieval and context recognition rely on distinct cognitive systems? One possibility is that solving these two tasks requires different computations. Context recognition likely involves identification of scenes or landmarks that a navigator can use to determine her general environmental context. Identification might be achieved by matching the contents of the current view with the contents of a previously stored view consisting of a combination of geometric and non-geometric information (Wang and Spelke, 2002). In this account, context recognition would be akin to object recognition, but performed on navigationally-relevant stimuli. By contrast, heading retrieval might involve interpreting the environment in terms of a spatial reference system from which orientational axes can be recovered (Cheng and Gallistel, 2005). While the precise computations underlying heading retrieval are unknown, previous work suggests that at least for humans heading retrieval is not performed by view-matching (Nardini et al., 2009; Lee and Spelke, 2011; Cheng et al., 2013). (See Appendix 3.2 for further consideration of the implications of the present experiments for view-matching theories of reorientation.)

Notably, previous work has identified a possible neuroanatomical basis for this behavioral dissociation. In humans, neuroimaging and neuropsychological work suggests that context recognition is primarily mediated by the parahippocampal place area (PPA), a region of medial occipitotemporal cortex that responds strongly when subjects view environmental scenes or landmark objects (Aguirre et al., 1998; Epstein and Kanwisher, 1998; Epstein and Vass, 2014b), whereas heading retrieval is primarily mediated by a system centered around the retrosplenial complex (RSC) in the medial parietal lobe (Epstein, 2008; Vann et al., 2009; Baumann and Mattingley, 2010; Vass and Epstein, 2013; Marchette et al., 2014b). Analogous to the current findings, the PPA appears to be sensitive to both geometric and non-geometric information (Epstein and Kanwisher, 1998; Dilks et al., 2011; Kravitz et al., 2011a; Park et al., 2011; Wolbers et al., 2011; Cant and Xu, 2012), whereas RSC appears to be especially sensitive to geometry when people retrieve spatial information from memory (Marchette et al., 2014b). In rodents, the homologous regions are postrhinal cortex (Burwell et al., 1995), which has been shown to be important for context recognition (Norman and Eacott, 2005), and retrosplenial cortex, which has
been shown to be important for deriving directional information from environmental cues (Pothuizen et al., 2008). Retrosplenial cortex contains head direction (HD) cells, which discharge selectively when the head of an animal is oriented in a particular facing direction (Taube, 1998), and a previous report demonstrated that these cells are primarily sensitive to environmental geometry rather than non-geometric features after disorientation (Knight et al., 2011). In addition, neurons that code allocentric locations relative to geometric boundaries have been identified in the entorhinal cortex (Solstad et al., 2008) and subiculum (Lever et al., 2009) of the rodent, and these cells might be important for retrieving the location of the reward within the chamber after chamber identity and heading have been re-established.

A possible caveat concerning our interpretation of the present experiments in terms of separable systems for context recognition and heading retrieval is that, as with any behavioral dissociation, we cannot know for certain the identity of the processes that we have dissociated. Although we think that context recognition and heading retrieval provide the most parsimonious descriptions of these processes, other accounts may also explain the data. For example, rather than distinguishing between the chambers as distinct environments, the animals might be distinguishing between two different situations that occur in the same environment, just as a person might distinguish between a wedding and a funeral that both occur in the same building. Although the spatial environment of both events is the same in this example, the contextual features surrounding each situation and the appropriate behaviors are different. Relatedly, we cannot know for certain that the second system supports retrieval of heading. An alternative possibility is that it codes egocentric locations relative to geometric boundaries, and that the animals choose their dig locations based on a strategy of approaching a corner with a particular local geometric configuration (e.g., short-wall left), without recovering heading at all. In addition, we emphasize once again that our results pertain to the mechanisms that allow the animal to recover its bearings after disorientation and do not necessarily provide insight into the mechanisms that allow the animal to maintain its bearings when oriented.
Finally, it is worth considering the implications of our findings for the ongoing debate about the nature of the cognitive mechanisms underlying spatial reorientation. Two theories are most prominent. The first theory builds on the classic results by arguing that reorientation is mediated by an encapsulated cognitive module (Fodor, 1983) that specifies a navigator’s position and orientation relative to the geometric structure of the environment but is insensitive to non-geometric features (Cheng, 1986; Gallistel, 1990; Hermer and Spelke, 1994). The second theory argues that a range of environmental cues, including both geometry and non-geometric features, can guide spatial reorientation (Learmonth et al., 2002; Cheng and Newcombe, 2005; Newcombe and Ratliff, 2007) and that the combination of cues used in any given situation can vary depending on their salience and reliability. Although our results might seem at first glance to fit more closely with the first view insofar as we postulate the operation of independent mechanisms, one of which is especially sensitive to geometry, it is important to note that our argument does not require that these two mechanisms be modular. More specifically, the dissociability of the context recognition and heading retrieval systems that we demonstrate here does not require heading retrieval to be impervious to non-geometric information under all circumstances. The key point is that we have found one set of circumstances in which non-geometric information is used for one function but not the other, thus establishing the independent operation of the two mechanisms. That said, if our conclusion that there are separate cognitive systems for context recognition and heading retrieval is correct, it may affect the interpretation of cue competition effects that have been taken as evidence in favor of non-modular theories (Gray et al., 2005; Pearce et al., 2006; Wilson and Alexander, 2008; Horne and Pearce, 2009; Horne et al., 2010b; Kosaki et al., 2013). In particular, some cue competition studies have observed that when animals learn to find a goal in a chamber containing both featural and geometric cues, and the featural cues are then altered or removed, then the animals are impaired at finding the goal. These findings have been interpreted as indicating that the learning of locations relative to featural cues can overshadow the learning of locations relative to geometric cues, in contradiction to the predictions of the modular theory. However, our results suggest an alternative account: when the featural cues are
changed, animals may believe that they are in a different place for which they do not know the location of the reward. Thus, some cue competition effects may be explained by the existence of a context recognition system that is sensitive to non-geometric features. Conversely, under this interpretation, the failure of a feature to interfere with learning based on environmental geometry (Hayward et al., 2003; Hayward et al., 2004; Doeller and Burgess, 2008; McGregor et al., 2009) may indicate that the feature did not form an integral part of the representation of that context.

In sum, our experiments demonstrate a dissociation between context recognition and heading retrieval in mice. Whereas context recognition is sensitive to both featural and geometric information, heading retrieval is primarily guided by spatial geometry. These findings indicate that context recognition and heading retrieval are mediated by different cognitive systems that operate with some degree of independence from each other. For a lost navigator to regain her bearings, she must solve not one but two problems, and both systems must work in concert to get her on her way.

2.5 Methods

Subjects. Distinct groups of 16 male C57BL/6 mice, 2-5 months old (Jackson Laboratory, Bar Harbor, ME), participated in the classical single-chamber paradigm, Experiment 1, and Experiment 2 (48 animals total). Mice were housed individually and kept on a 12-hour light/dark cycle for at least two weeks prior to the beginning of the experiments. They had access to water ad libitum, but to increase motivation to participate in the task, they were maintained at 85%-90% of their free-feed weight. Starting four days prior to the experiment, animals were shaped to dig in a medicine cup for a food reward (Kellogg's Cocoa Krispies) in their home cage by providing them once daily with the reward gradually buried deeper under scented bedding. Animal living conditions were consistent with the standards set forth by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). All experiments were approved by the
Institution of Animal Care and Use Committee of the University of Pennsylvania, and were conducted in accordance with NIH guidelines.

**Apparatus.** The classical single-chamber experiment was conducted in a rectangular (20 x 30 x 25 cm) chamber. Experiments 1 and 2 were both conducted in two geometrically identical rectangular (20 x 30 x 25 cm) chambers. The walls and floor of all chambers were covered in white laminate. In the single-chamber experiment, there were three black stripes (either vertical or horizontal, balanced across animals) along one short wall (Fig. 2.1A). In Exp. 1, the two chambers were distinguished by three black stripes along the short wall, which were vertical in one chamber and horizontal in the other (Fig. 2.2A). In Exp. 2, chambers were distinguished by the location of three vertical black stripes, which were placed along the short wall in one chamber and in the center of the long wall in the other (Fig. 2.3A). In all experiments, stripes were 4 cm in width. Testing in all chambers occurred in the same location in the experimental room. The chambers were surrounded by a square black curtain with rounded corners, were uniformly lit from overhead, and a white noise generator was hung centrally above the chamber to ensure that animals could not use extraneous sounds as beacons. Cups were embedded in each of the four corners of the chamber floors. The cups contained odor-masked bedding, consisting of 1g of odor mask (either ground cumin or ginger) for every 100g of bedding. Mouse behavior was recorded using LimeLight video tracking system (Coulbourn Instruments, USA) via an overhead, centrally located camera.

**Design and Procedure.** A pilot experiment showed that mice could discriminate the horizontal and vertical stripes to a performance criterion of 75% correct after 8 training trials. Thus, all experiments began with a training phase consisting of 4 training trials per chamber per day for two days, with successive trials alternated across chambers (8 trials total in the one chamber experiment, 16 trials total in the two chamber experiments). During this training, mice were taught to search for a reward, which was visible for the first two training trials per chamber and buried in
the remaining training trials. In the single-chamber experiment, the reward was always located in one of the two corners nearest the striped feature. In Experiments 1 and 2, the reward was always located in one of these two corners in one chamber, and in the other feature-adjoining corner in the other chamber. These locations were counterbalanced across animals; however, for all analyses and figures the percentage of searches at each corner are reflected such that correct corner is the same for all animals.

Animals were disoriented prior to the start of every trial. To disorient an animal, it was placed in a PVC cylinder with a detachable base and lid. The experimenter slowly rotated the cylinder on a turntable roughly four full clockwise then four full counterclockwise revolutions. The cylinder was then carried to the chamber and the base was slid out from underneath the animal. The cylinder was lifted to start a trial. To ensure that the animals could not use any room cues that were not completely eliminated by use of a surrounding curtain and a white-noise generator, chambers were rotated 90° or 180° prior to each trial, counterbalanced so that all orientations relative to the room were experienced equally often. The chambers were cleaned with ethanol at the end of each trial to remove odor trails. The inter-trial interval was 3-5 minutes.

Following training, animals were tested in one session per day for four days. In the single chamber experiment, testing sessions consisted of two rewarded and two unrewarded trials (interleaved). In Exps. 1 and 2, testing sessions consisted of two rewarded and two unrewarded trials per chamber. Thus, in all cases, there were a total of 16 test trials per chamber. In Exps. 1 and 2, chambers were tested in an interleaved fashion, as were the rewarded and unrewarded trials. So, a sequence for one session might be: Chamber 1 (rewarded), Chamber 2 (rewarded), Chamber 1 (unrewarded), Chamber 2 (unrewarded), etc. The order in which chambers were tested was counterbalanced across sessions. During reward trials, mice were removed from the apparatus after they had found the reward. During unrewarded trials, they were removed after their first dig, or after 45 seconds (whichever came later). Digs were counted whenever an animal removed bedding from a cup using one or both paws. Unrewarded trials were included to train the mice to concentrate their first dig at the reward location and as a control for the possibility that
mice could smell the reward during rewarded trials. However, there was no difference in the distribution of first digs across corners between rewarded and unrewarded trials in the classical single-chamber experiment ($\chi^2(3) = 4.67, p = 0.20$), Exp. 1 ($\chi^2(3) = 0.70, p = 0.87$), or Exp. 2 ($\chi^2(3) = 5.44, p = 0.14$). Therefore, we collapsed across rewarded and unrewarded trials for all analyses.

Dig locations were coded following testing by an experimenter blind to condition. The dependent measure was the first corner in which the animal dug. Paired sample t-tests were used to assess whether the proportion of digs were distributed in the chambers according to the geometry. For Exps. 1 and 2, repeated measures ANOVA with absolute corner location (long wall left or right) and chambers as within-subjects factors were used to compare the search behavior across chambers. All reported statistics are based on two-tailed significance tests.

The day following the final Exp. 2 testing session, 15 of the 16 animals that participated in Exp. 2 were then run in a control experiment in which the animal’s search behavior was observed in two square chambers, one large (30 x 30 x 25 cm) and one small (20 x 20 x 25 cm). Cups were embedded in each of the four corners of the chamber floors. Both chambers had the same vertical stripe feature along one wall that used in Exp. 2. There were four interleaved probe trials per square. Every trial per chamber, the chambers were rotated 90° or 180°. Animals were disoriented prior to the start of each trial.
Figure 2.1. Design and results for the preliminary experiment, which used the classical one-chamber reorientation paradigm. A) Disoriented mice were trained to locate a reward in a single rectangular chamber with a visual feature along one short wall. C, R, N, and F denote the four cups in the corners of the chamber, where C denotes the correct corner (i.e., the corner with the hidden reward), R the rotationally equivalent corner (i.e., the corner geometrically equivalent to C), N the near corner (i.e., the corner that is closest to C), and F the far corner (i.e., the non-rotationally equivalent corner farthest from C). B) Percentage of first digs in each of the four corners of the chamber (and SEMs). The star denotes the rewarded location. Mice searched significantly more often at C and R (bolded) than N and F, but there was no significant difference between the percentage of digs at C and R. This reprises the classical results.
Figure 2.2. Design and Results for Experiment 1. A) Mice were trained to locate a hidden reward in two rectangular chambers that had identical geometry but were distinguishable by the orientation of stripes (vertical vs. horizontal) along a single short wall. C, R, N, and F denote the four cups in the corners of the chambers, where C denotes the correct corner, R the geometrically equivalent corner, N the near corner, and F the far corner. Note that the location of the rewarded cup differed between the two chambers. B) Shows the average percentage of first digs (and SEMs) in each corner of the two chambers. Stars denote the rewarded locations; bolded numbers indicate digs in geometrically appropriate corners. C) The bar chart shows the same data as in B, but averaged over geometrically equivalent corners. Error bars denote +/- 1 SEM. Mice dug more often in the corners that were geometrically appropriate for each chamber, thus indicating that they distinguished between the chambers. Moreover, they did not distinguish between geometrically appropriate corners. * p < 0.05, *** p < 0.001.
Figure 2.3. Design and Results for Experiment 2. A) The design was the same as Experiment 1, but in this case the two chambers were distinguished by the location of vertical stripes either on the short wall or the long wall. B) Shows the average percentage of first digs (and SEMs) in each corner of the two chambers. Stars denote the rewarded locations; bolded numbers indicated digs in geometrically appropriate corners. C) The bar chart shows the same data as in B, but averaged over geometrically equivalent corners. Error bars denote +/- 1 SEM. Mice dug more often in the corners that were geometrically appropriate for each chamber, thus indicating that they distinguished between the chambers. Moreover, they did not distinguish between geometrically appropriate corners. ** p < 0.01, *** p < 0.001.
Figure 2.4. Results from the square chambers. Following the last day of testing in Experiment 2, disoriented animals were tested in two square chambers with a vertical striped feature along one wall. The average percentage of first digs (and SEMs) at each corner in both size square chambers is shown. The star denotes the location that was correct relative to the feature in the rectangular chambers in Exp. 2. The animals did not go to the “correct” cup in this case. This indicates that they did not use a response-based strategy of choosing the cup on the appropriate side of the feature irrespective of context.
CHAPTER 3: The Occipital Place Area is causally involved in representing environmental boundaries during navigation


3.1 Abstract

Thirty years of research suggests that environmental boundaries—e.g. the walls of an experimental chamber or room—exert powerful influence on navigational behavior, often to the exclusion of other cues (Cheng, 1986; Gallistel, 1990; Wang and Spelke, 2002; Hayward et al., 2003; Hartley et al., 2004; Doeller and Burgess, 2008; McGregor et al., 2009; Cheng et al., 2013; Julian et al., 2015). Consistent with this behavioral work, neurons in brain structures that instantiate spatial memory often exhibit firing fields that are strongly controlled by environmental boundaries (O'Keefe and Burgess, 1996; Doeller et al., 2008; Solstad et al., 2008; Lever et al., 2009; Stewart et al., 2014; Krupic et al., 2015). Despite the clear importance of environmental boundaries for spatial coding, however, a brain region that mediates the perception of boundary information has not yet been identified. We hypothesized that the Occipital Place Area (OPA), a scene-selective region located near the transverse occipital sulcus (Dilks et al., 2013), might provide this perceptual source by extracting boundary information from visual scenes during navigation. To test this idea, we used transcranial magnetic stimulation (TMS) to interrupt processing in the OPA while subjects performed a virtual-reality memory task that required them to learn the spatial locations of test objects that were either fixed in place relative to the boundary of the environment or moved in tandem with a landmark object. Consistent with our prediction, we found that TMS to the right OPA impaired spatial memory for boundary-tethered but not landmark-tethered objects. Moreover, this effect was found when the boundary was defined by a wall, but not when it was defined by a marking on the ground. These results show that the OPA is causally involved in boundary-based spatial navigation and suggest that OPA is the perceptual source of the boundary information that controls navigational behavior.
3.2 Results

In Experiment 1, we tested the causal role of the OPA in boundary-based navigation by using TMS to interrupt processing in the OPA while participants (n=12) learned the locations of four test objects inside a virtual arena (3.3 Methods). Following the behavioral paradigm pioneered by Doeller and colleagues (2008), on each trial subjects saw a word denoting one of the test objects and indicated its location by navigating to it from a random start location and making a button-press response (the "replace" phase; Fig. 3.1A) (Doeller et al., 2008). Participants were then teleported to a random position and the object appeared in its correct location and was collected (the "feedback" phase). The arena was limited by a circular boundary wall and contained a rotationally-symmetric landmark object; it was also surrounded by distal cues (mountains and sky, rendered at infinity). Thus, the distal cues could be used to determine heading, but locations within the arena could only be defined based on distances to the bounding wall or the landmark object.

A set of 16 trials (four per experimental object) composed a block, and there were three blocks in the experiment. Critically, the landmark object was moved relative to the boundary between blocks 1 and 2 and again between blocks 2 and 3. Two test objects maintained their locations relative to the boundary after these moves and two maintained their locations relative to the landmark (Fig. 3.1B). Within and across blocks, participants learned the relationships between object locations and the landmark or boundary by using the feedback provided. This design allowed us to assess learning of object location relative to each cue independently. Prior to each block we applied continuous theta burst transcranial magnetic stimulation (cTBS; three-pulse bursts at 50 Hz repeated every 200ms for 40s) (Huang et al., 2005) to either the right OPA or a Vertex control site (see 3.3 Methods; Fig. 3.2A). Each subject received stimulation to both TMS sites in two sessions separated by one week, with stimulation order counterbalanced across subjects. The OPA was functionally defined in each subject based on fMRI data obtained in a separate experimental session.

We focused on the OPA as a potential source for the boundary signal because it is one of
three brain regions that respond selectively in fMRI during the visual perception of scenes (e.g. landscapes, streets, rooms) (Nakamura et al., 2000; Grill-Spector, 2003; Hasson et al., 2003; Levy et al., 2004; Dilks et al., 2013). We conjectured that this scene-preferential response might be driven in part by analysis of boundary surfaces, as the presence of such surfaces is one of the primary characteristics that distinguish scenes from non-preferred stimuli such as single objects and faces (Henderson and Hollingworth, 1999; Epstein, 2005). Previous fMRI work has shown sensitivity to boundaries in the two other scene-responsive regions—the parahippocampal place area (PPA) and retrosplenial complex (RSC)—but several aspects of the literature suggest that these regions might not be the ultimate source of the boundary signal. In particular, although the PPA responds to the presence of boundaries (Epstein and Kanwisher, 1998; Committeri et al., 2004) and represents the shape of the space as defined by boundaries (Kravitz et al., 2011a; Park et al., 2011), it is also sensitive to non-boundary scene elements that are useful for context recognition such as surface textures and landmark objects (Schinazi and Epstein, 2010b; Cant and Xu, 2012; Harel et al., 2013; Vass and Epstein, 2013). Similarly, RSC codes location and heading relative to boundaries (Marchette et al., 2014b), and the spatial extent of the bounded space in a scene (Park et al., 2014); however, the RSC is believed to play a primarily mnemonic role in spatial navigation and thus is unlikely to be the source of the perceptual boundary signal (Epstein, 2008; Vann et al., 2009). In contrast, the function of OPA is believed to be perceptual, thus making it a more likely candidate.

Performance during Exp. 1 was assessed by measuring the distance between each object’s replaced location and the correct location (Fig. 3.1C). We analyzed data from block 1 separately from the data from blocks 2 and 3, as the critical distinction between boundary-tethered and landmark-tethered objects is not made until the later blocks. In block 1, a 2x2x4 ANOVA with factors for stimulation site (OPA vs. vertex), object type (boundary-tethered vs. landmark-tethered), and trial (1-4) found no effects of stimulation site (F(1,11)=0.15, p=0.71) and—as expected by design—no effect of object type (F(1,11)=0.02, p=0.90). There was marginal improvement in performance across trials (F(3,33)=2.65, p=0.07, ηp²=0.19) as a result of
the feedback. Performance was noticeably better in this block than in subsequent blocks, which is not surprising because in block 1 participants could use both the boundary and the landmark as references to code the location of each target object and there was no conflict between these two cues.

We next assessed performance during blocks 2-3, in which the relative movement of the boundary and landmark caused the two cues to indicate different locations. In this case, we conducted an analogous ANOVA with block (2-3) as an additional factor, summarized in Table 3.1 and below. There was a main effect of object type (F(1,11)=7.09, p=0.02, $\eta^2_p = 0.39$), with greater error for the boundary- than landmark-tethered objects, and a main effect of stimulation site (F(1,11)=14.76, p=0.003, $\eta^2_p = 0.57$), with greater error during the OPA than Vertex sessions. Critically, there was a significant interaction between stimulation site and object type (F(1,11)=10.14, p=0.009, $\eta^2_p = 0.48$): compared to Vertex, participants were significantly impaired when replacing the boundary-tethered objects ($t(11)=3.80$, p=0.003; all pairwise tests 2-tailed unless otherwise noted), but there was no difference in performance between stimulation sites for the landmark-tethered objects ($t(11)=0.23$, p=0.82). Thus, consistent with our predictions, TMS to OPA specifically impaid the ability to navigate to locations defined by reference to boundaries. This impairment could reflect a deficit in perceiving boundaries during the encoding stage of each trial, the retrieval stage, or both.

The specific impairment for boundary-tethered objects after OPA stimulation was not due to the task being inherently more difficult for these objects: performance levels did not differ significantly between the boundary- and landmark-tethered objects during the Vertex sessions ($t(11)=1.77$, p=0.11). Nor was it due to an impairment in sensitivity to feedback in general: there was no interaction between stimulation site and trial (F(3,9)=1.39, p=0.35) or block (F(1,11)=0.54, p=0.48). Nor was it due to a speed-accuracy trade-off: there was no interaction between stimulation site and object type in response time (RT) during the replace or feedback phases (both F(1,11)s < 1.0, both ps > 0.34; Fig. 3.2C). Path length and path tortuosity were also both matched between stimulation sites, indicating that motor and planning aspects of the task were
unimpaired by TMS to OPA (both $F(1,11)s < 1.35$, both $ps > 0.27$; Fig. 3.2C). Thus, subjects performed the task in the same manner after OPA stimulation and learned at a similar rate, but their ability to use boundary information for spatial memory was reduced, consistent with a boundary-specific perceptual deficit.

During blocks 2-3, the landmark and boundary predict conflicting target object locations. If boundary information is perceived as less reliable following OPA stimulation, then OPA stimulation may cause a bias to use the landmark to replace the target objects. To examine if performance errors could be explained in part by over-reliance on the landmark, we computed the relative influence of the landmark on the replace locations during blocks 2-3 (Fig. 3.3A). A 2x2x2x4 ANOVA with factors for stimulation site, object type, block, and trial revealed increasing landmark influence on the landmark-tethered objects, and decreasing landmark influence on the boundary-tethered objects, across blocks ($F(1,11)=12.81; p=0.004, \eta_{p}^2 = 0.54$) and trials ($F(3,33)=27.76; p < 0.001, \eta_{p}^2 = 0.72$) (Fig. 3.2B; see also Table 3.1). Thus, participants learned the associations between the target objects and the appropriate cue. Importantly, however, the landmark had greater influence during the OPA than the Vertex sessions ($F(1,11)=6.45; p=0.03, \eta_{p}^2 = 0.37$), indicating a shift towards use of the landmark after OPA stimulation. This shift was found for the boundary-tethered objects ($t(11)=2.60, p=0.03$), but not the landmark-tethered objects ($t(11)=0.23, p=0.55$), although the interaction between object type and stimulation site was not significant ($F(1,11)=1.01; p=0.34$). Notably, overall landmark influence during the Vertex sessions was significantly correlated across participants with the magnitude of the boundary-specific memory impairment during the OPA stimulation sessions ($r^2=0.72, p < 0.001$; Fig. 3.2B). Thus, when OPA is disrupted, subjects are more likely to use the landmark to localize the objects, despite the fact that this is an inappropriate reference for the boundary-tethered objects; moreover, this increase in landmark influence is greatest in subjects who are already most inclined to use the landmark. These results are consistent with previous work indicating that the neural systems that mediate boundary- and landmark-based navigation interact with one another to guide spatial behavior (Poldrack et al., 2001; Doeller et al., 2008).
What information about boundaries does the OPA encode? There are at least two possibilities. First, the boundary and landmark differ in their physical structure: the boundary is an extended surface, whereas the landmark is a discrete object. Second, the boundary takes up a larger retinotopic extent than the landmark. It is possible that the OPA codes large-scale visual information, rather than boundaries specifically. Indeed, previous studies have reported that OPA has a peripheral visual bias (Levy et al., 2001; Levy et al., 2004). To distinguish between these alternatives, we ran a second experiment in which participants (n=12) learned the locations of objects inside two distinct circular arenas using the same replace/feedback trial structure as in Exp. 1 (Fig. 3.1A). The first arena was surrounded by a wall as in Exp. 1 ("Wall Arena"), whereas the second had no wall but consisted of a visual texture (or "mat") drawn on the ground ("Mat Arena") (Fig. 3.4A; 3.3 Methods). The two arenas had the same diameter, were visually identical except for the presence of the surface boundary, and were surrounded by the same distal orientational cues, rendered at infinity. Unlike in the Wall Arena, participants could walk outside the edges of the mat; thus, the edge of the mat did not provide a "boundary" in the sense of being a bounding surface that obstructed movement, though it did provide a reference for localizing the object. In contrast to Exp. 1, there was no landmark object present, so in this case participants had to rely exclusively on the arena edge to determine target object position. For each arena, all trials (3 for each object; 12 total) were presented within a single block, with arena order counterbalanced across participants. (Participants were also tested in a third arena in which the boundary was defined by a water barrier that blocked movement but results from this condition were inconclusive; see 3.3 Methods.) Prior to each block we applied cTBS to either the functionally-defined right OPA or a Vertex control site (Fig. 3.5A). Each subject received stimulation to both TMS sites in two sessions separated by one week with stimulation order counterbalanced across subjects.

A 2x2x3 ANOVA, with factors for stimulation site (OPA vs. Vertex), arena (Wall vs. Mat), and trial (1-3), revealed no main effects of arena type (F(1,11)=0.12, p=0.63) or stimulation site (F(1,11)=0.25, p=0.74) but did reveal improvement of performance across trials (F(2,10)=5.48,
p=0.01, $\eta_p^2 = 0.33$) (Fig. 3.3B; see also Table 3.3). Critically, there was a significant interaction between arena and stimulation site ($F(1,11)=5.97$, $p=0.03$, $\eta_p^2 = 0.35$): OPA stimulation significantly impaired performance in the Wall Arena relative to Vertex ($t(11)=2.36$, $p=0.04$), replicating the results of Exp. 1, but did not significantly affect performance in the Mat Arena ($t(11)=1.17$, $p=0.27$). Control analyses further found that the wall-selective impairment following OPA stimulation was not due to i) an impairment in overall sensitivity to feedback, as there was no interaction between stimulation site and trial (Fig. 3.4B), nor ii) an interaction between arena type and stimulation site in RT (Fig. 3.5C), nor iii) an effect of stimulation site on path length or path tortuosity (Fig. 3.5C) (all $F$s < 0.89, all $p$s > 0.35). Thus, stimulation of OPA disrupts coding of locations relative to bounding surfaces, but not relative to large-scale visual information generally. Moreover, the fact that stimulation of OPA impaired performance on the Wall Arena even though no landmark was present implies that OPA stimulation impairs the quality of the boundary representation itself, rather than simply causing a bias to rely on non-boundary cues.

3.3 Discussion

Our results indicate that the OPA is causally involved in the coding of object locations relative to environmental surface boundaries. Stimulation of OPA impaired accurate navigation to boundary-tethered but not landmark-tethered objects in Experiment 1. Furthermore, this impairment was only observed in Experiment 2 when the boundary of the arena was defined by a wall, not when it was defined by a marking on the ground.

These findings have important implications for our understanding of the neural basis of spatial navigation. There is extensive behavioral evidence that boundaries are a very salient navigational cue (Cheng, 1986; Gallistel, 1990; Wang and Spelke, 2002; Hayward et al., 2003; Hartley et al., 2004; Doeller and Burgess, 2008; McGregor et al., 2009; Cheng et al., 2013; Julian et al., 2015), and boundary-related spatial coding has been identified in several brain structures, including the hippocampal formation (O'Keefe and Burgess, 1996; Doeller et al., 2008; Solstad et
al., 2008; Lever et al., 2009; Bird et al., 2010; Stewart et al., 2014; Krupic et al., 2015) and RSC (Marchette et al., 2014b). However, the perceptual source of this boundary information has remained a mystery. Our results suggest that OPA may be that perceptual source. This conclusion dovetails with recent findings that OPA is sensitive to ‘sense’ (left/right) and distance information in visual scenes (Dilks et al., 2011; Persichetti and Dilks, 2016), and is involved in making spatial judgments about object locations (Nasr et al., 2013). Moreover, the fact that stimulation of OPA does not disrupt memory for locations defined by a marking on the ground is consistent with previous observations that the navigation system that codes locations relative to environmental geometry is often insensitive to large-scale non-boundary features (Lee and Spelke, 2011; Lee et al., 2012b).

Although the precise connectivity of the OPA remains unknown, there are at least two possible pathways by which this boundary information might be communicated to the network of brain regions implicated in spatial navigation, as discussed in Chapter 1. First, the OPA and PPA are functionally connected (Baldassano et al., 2013; Rafique et al., 2015), and the PPA may serve as an intermediate input to the hippocampal formation (Naber et al., 1997; Ho and Burwell, 2014). Second, the OPA may provide boundary information to the adjacent posterior parietal cortex, which projects to the RSC, PPA, and hippocampus (Kravitz et al., 2011b; Baldassano et al., 2013). It also remains possible that the current results might be obtained by the use of a view-matching strategy where the views are defined exclusively by boundaries but not other visual features. In this case, a connection between OPA and the broader navigational system would not be required. However, we think that this explanation is unlikely, as previous work suggests that people solve similar tasks by coding object location relative to boundaries, not by view-matching (Hartley et al., 2004).

In addition to demonstrating that the OPA is critical for boundary-based navigation, our results also provide insight into the functional organization of the human visual system. The OPA forms a central node in the cortical network for scene perception, along with the PPA and RSC, and previous fMRI and TMS research has highlighted the importance of OPA in scene-specific
processing (Nasr et al., 2011; Bettencourt and Xu, 2013; Dilks et al., 2013; Ganaden et al., 2013; Marchette et al., 2015a). Compared to PPA and RSC, however, the precise function of the OPA has been less well explored. By implicating the OPA in the perception of environmental boundaries, our results suggest a potential function for this region that might explain its preferential response to scenes; namely, the OPA may respond selectively to scenes because such stimuli tend to depict navigational boundaries.

These results raise an important set of new questions regarding the function of OPA in boundary-based navigation. First, is OPA only involved in the perception of surface boundaries, or does it also serve a mnemonic function, both of which would have been disrupted by TMS in the present experiments? Although we prefer a perceptual account, we cannot rule out a mnemonic role for OPA based on the current data alone. Second, does OPA encode explicit representations of bounding geometry or does it merely extract mid-level visual features that allow boundary representations to be constructed by downstream regions? Third, is OPA involved in the coding of non-surface boundaries? We attempted to address this third question in Experiment 2, but the results were inconclusive (see 3.3 Methods). We suspect that OPA may be involved in the coding a wide range of environmental features that define the navigational affordances of local space, not just surface boundaries, but this remains to be established.

3.3 Methods

Participants. Two groups of twelve participants gave written consent and were paid for participating in Exp. 1 (5 female, mean age 23, age range 20-28) and Exp. 2 (4 female, mean age 24, age range 19-33). Five subjects participated in both experiments, separated by roughly six months. All had normal or corrected-to-normal vision and reported to be in good health with no history of neurological disease. All subjects provided informed consent in accordance with the Institutional Review Board of the University of Pennsylvania.
fMRI Localization of the OPA. Prior to TMS, each participant completed an fMRI localizer scan to localize the right OPA. Scanning was performed at the Hospital of the University of Pennsylvania using a 3T Siemens Trio scanner equipped with a 32-channel head coil. High-resolution T1-weighted images for anatomical localization were acquired using a three-dimensional magnetization-prepared rapid acquisition gradient echo pulse sequence [repetition time (TR), 1620 ms; echo time (TE), 3.09 ms; inversion time, 950 ms; voxel size, 1 x 1 x 1 mm; matrix size, 192 x 256 x 160]. T2*-weighted images sensitive to blood oxygenation level-dependent contrasts were acquired using a gradient echo echoplanar pulse sequence (TR, 3000 ms; TE, 30 ms; flip angle 90°; voxel size, 3 x 3 x 3 mm; field of view, 192; matrix size, 64 x 64 x 44). Visual stimuli were displayed by rear-projecting them onto a Mylar screen at 1024 x 768 pixel resolution with an Epson 8100 3-LCD projector equipped with a Buhl long-throw lens. Subjects viewed the images through a mirror attached to the head coil.

During scanning, subjects completed two functional localizer scans. The localizer procedure was identical to the procedure used in prior reports (e.g., Marchette et al., 2015a). These scans were each 5 min 21 s in length, during which subjects performed a 1-back repetition detection task on color images of faces, scenes, objects, and scrambled objects, presented in 16 s blocks with each stimulus shown for 600 ms each with a 400 ms interstimulus interval. Images subtended a visual angle of approximately 9.0° x 9.0°.

Data from the localizer scans were analyzed with the FMRIB Software Library (FSL) using the following steps. First, they were corrected for differences in slice timing by resampling slices in time to match the first slice of each volume. Second, they were corrected for subject motion by realigning to the first volume of the scan run using MCFLIRT (Jenkinson et al., 2002). Third, the timecourses for each voxel were high-pass filtered to remove low temporal frequency fluctuations in the BOLD signal that exceeded lengths of 100 s. Data were then spatially smoothed with a 5 mm full-width at half-maximum Gaussian filter. A GLM consisting of a boxcar regressor convolved with a standard double gamma function was then used to model the fMRI response to each stimulus condition. The scene-selective right OPA was identified in each
participant by overlaying individual scenes > objects contrast maps on high-resolution MRI scans for each participant. The anatomical location of the right OPA, near the transverse occipital and intraparietal sulci, was confirmed using standard methods (Julian et al., 2012) (Figs. 3.2A and 3.5A).

**Stimulation Sites and Transcranial Magnetic Stimulation.** TheBrainsight system (Rogue Research, Montreal) was used to co-register MRI data with the location of the subject and the TMS coil. The OPA stimulation site was defined in each participant by selecting the voxel exhibiting peak scene-selectivity (i.e., the highest t-value from the scenes > objects contrast) in the right OPA. The Vertex control site was identified in each participant as the midpoint between the bridge of the nose and the inion, and between the temples. A Magstim Super Rapid\(^2\) Plus\(^1\) stimulator (Magstim; Whitland, UK) was used to deliver cTBS via a 70 mm diameter figure-eight coil. For OPA stimulation, the TMS coil handle was held pointing upwards. To calibrate the intensity of stimulation, cTBS was delivered at 80% of each participant’s phosphene threshold. Each participant’s phosphene threshold was determined prior to the start of the first experimental session using a standard up-down staircase procedure with stimulation to visual area V1 (Kammer and Beck, 2002).

For both experiments, each subject participated in two testing sessions separated by one week, one for each of the two stimulation sites (counterbalanced across subjects). In Exp. 1, stimulation was applied immediately prior to each testing block, and in Exp. 2 stimulation was applied five minutes prior to each testing block.

**Virtual Reality Environments and Testing Procedure.** We used Source SDK Hammer Editor (http://www.valvesoftware.com, Valve Software, Bellevue, WA) to construct a virtual reality environment that was rendered and displayed from the first person-perspective using the commercial game software Portal (http://www.valvesoftware.com, Valve Software, Bellevue, WA). The environment was displayed on a 27-inch LG monitor (resolution: 1920 x 1080) and
participants were seated roughly 50 cm from the screen. In both experiments, participants learned the locations of target objects inside an arena in the virtual environment, using the learning procedure illustrated in Figure 1A. Participants moved through the arena by using their right hand to operate arrow keys to move forward or backwards and turn left or right. Responses during the replace phase were collected by participants pressing the “e” key with their left hand. Virtual heading and location were recorded every 100 ms.

In Exp. 1, participants were tested inside an arena consisting of a landmark object surrounded by a circular boundary wall. The boundary wall was 130 virtual units (vu) in diameter, and 10 vu in height relative to a simulated eye-level of 4 vu. One virtual unit corresponds to 0.3048 real-world meters (1 foot). The landmark object was either a trashcan or a metal ball, counterbalanced across TMS target sites. The complete set of target objects was either [coffee table, propane tank, barrel, traffic cone] or [radiator, lamp, oil drum, cake], counterbalanced across TMS target sites. The target objects for each trial were selected in pseudo-random order. Prior to the start of the first replace phase during block 1, but not blocks 2-3, participants collected each target object in pseudo-random order twice (i.e., performed the feedback phase twice per target object) in order to learn the locations of the objects.

In Exp. 2, participants were tested in two different circular arenas: Wall and Mat. The Wall Arena surrounded by a wall as in Exp. 1. The Mat Arena consisted of a visual texture (or “mat”) drawn on the ground. Both the Wall and Mat arenas had the same visual texture drawn on the ground; thus, the Wall and Mat arenas were visually identical except for the presence of the boundary. The Wall and Mat Arenas had the same diameter as the Exp. 1 arena. The boundary wall in the Wall Arena was 4 vu in height, which is shorter than the boundary wall in Exp. 1 so that the visibility of the distal cues were better matched between the Wall and Mat Arenas. Participants could walk beyond the edge of the mat in the Mat Arena, and were instructed that they could do so. However, participants only spent an average of 4.7% of the total testing time beyond the edge of the mat, and there was no difference in time spent outside the mat edge between the OPA and Vertex sessions ($t(11)= 0.20, p > 0.5$). The complete set of target objects
in the Wall Arena was either [basketball, hairdryer, arm chair, refrigerator] or [cooler, binoculars, computer monitor, hat]. The complete set of target objects in the Mat Arena was either [washer, calculator, bench, cabinet] or [vacuum, bowling ball, cell phone, stapler]. Target object sets were counterbalanced across TMS target sites for each arena. The target objects for each trial were selected in pseudo-random order. Prior to the start of the first replace phase in each arena, participants collected each target object in pseudo-random order twice (i.e., performed the feedback phase twice per target object).

In addition to the Wall and Mat Arenas in Exp. 2, participants were also tested in a third arena: the Island (Fig. 3.5B). The Island consisted of a circular island surrounded by “water” that impeded movement. This arena was included to examine if the OPA codes boundaries defined solely by their impediment to movement, and not just surface boundaries. Prior to testing in the Island arena, participants were informed that they could not walk beyond the island edge. The complete set of target objects in the Island Arena were [bottle, piano, football, coffee maker] or [treadmill, vase, soccer ball, sofa], counterbalanced across TMS target sites. In the Island, we observed no difference in overall performance between the OPA and Vertex sessions ($t(11)=0.10, p > 0.5$). However, performance in this arena was confounded with response time: participants took significantly more time to replace the objects following OPA stimulation than after stimulation of Vertex ($t(11) = 2.36, p < 0.05$). Further, 10 out of 12 participants took longer to collect the target objects during the feedback phase following OPA stimulation compared to Vertex ($p < 0.05$, sign-test), although one participant went strongly in the opposite direction. Thus, results from this experiment were ambiguous: on the one hand, the absence of an accuracy difference suggests that OPA might not be involved in processing boundaries that are defined by an obstacle at ground level rather than a wall; on the other hand, the fact that response times were longer after OPA stimulation suggests that an impairment in accuracy may have been masked by a speed-accuracy tradeoff. Because of the ambiguity of the results, data from the Island were omitted from further analyses.
Figure 3.1. Experiment 1 Primary Methods and Results. A) Trial structure (after initial learning of object locations in block 1, see 3.3 Methods). On each trial, participants navigated to the remembered location of the target object ("replace" phase) and, after a short delay with a black screen, received feedback ("feedback" phase). Top shows a map of the virtual trajectory taken by the participant on each phase of a typical trial, and bottom shows example views of the virtual environment from the participant’s perspective. The name of the target object remained on the center of the screen during the entire trial. B) Participants learned four object locations over three blocks. The landmark was moved relative to the boundary at the start of block 2, and again at the start of block 3. Two objects were tethered to the landmark (red dots) and two objects were tethered the boundary (blue dots). TMS was applied to either the OPA or a Vertex control site prior to the start of each block. C) Top row shows the average distance error for the landmark-tethered objects (in red) and bottom row shows the average distance error for the boundary-tethered object (in blue) during the replace phase. Vertex sessions are in light colors and OPA sessions are in dark colors. Distance error is the distance between the replace location and the correct location for each trial, averaged over the two objects paired with each cue, in virtual units (VU). Compared to Vertex, participants were significantly impaired at replacing the boundary objects following OPA stimulation, but not the landmark objects. Significance markers indicate the strength of the difference between OPA and Vertex for each object type and block (1-tailed t-test; ** p < 0.01, * p < 0.05). Error bars indicate ±1 SEM.
Figure 3.2. Experiment 1 Additional Methods and Results. A) The group-based right Occipital Place Area (OPA) derived from a large number (42) of subjects across several studies from our laboratory, shown in green on the average cortical surface (Julian et al., 2012). The OPA TMS target site was defined for each participant as the OPA voxel exhibiting peak scene-selectivity. Each red dot denotes an OPA target site for a single participant in Experiment 1 (mean Talairach coordinates: [34, -77, 21]). B) Correlation between overall landmark influence during the Vertex session and boundary-specific memory impairment (i.e., boundary-tethered object distance error minus landmark-tethered object distance error) during the OPA session across participants. C) Mean path length and path tortuosity during the replace phase, and mean response time during both the replace phase and feedback phase, separately for the OPA (dark colors) and Vertex (light colors) sessions for the landmark- (L; in red) and boundary-related (B; in blue) objects (±1 SEM). Path tortuosity for each trial was computed as the path length divided by the Euclidean distance between the starting and end location of the path taken by the participant. Separate 2(object type: landmark-tethered vs. boundary-tethered) x 2(stimulation site: OPA vs. Vertex) ANOVAs revealed no significant main effects or interactions for path length, or response time during the replace or feedback phases (all $F(1,11)$s < 2.25, all $p$s > 0.1). Path tortuosity was marginally lower for the landmark-tethered than boundary-tethered objects ($F(1,11) = 4.15, p=0.07$), but critically there was no significant main effect of stimulation site or interaction (both $F(1,11)$s < 1.35, both $p$s > 0.27).
Figure 3.3. Influence of the landmark on replace locations in Experiment 1. A) The relative influence of the landmark was calculated as $d_B/(d_L + d_B)$, where $d_L$ is the distance of the response from the target location previously associated with the landmark and $d_B$ is the distance of the response from the target location previously associated with the boundary. This measure ranges from 0 to 1, where 0 is complete influence of the boundary and 1 is complete influence of the landmark. For block 3, two target locations were associated with the boundary for landmark-tethered objects, one from block 1 and the other from block 2, and so we used the location associated with the lowest $d_B$. B) Top row shows the relative influence of the landmark on landmark-tethered objects (in red) and bottom row shows the relative influence of the landmark on boundary-tethered objects (in blue). Vertex sessions are in light colors and OPA sessions are in dark colors. Over the course of each block and trial, participants became more likely to use the landmark to localize landmark-tethered objects and less likely to use the landmark to localize boundary-tethered objects. Compared to Vertex, participants were more likely to be influenced by the landmark after OPA stimulation. Significance markers indicate the strength of the difference between OPA and Vertex for each object type and block (1-tailed t-test; * $p < 0.05$, † $p < 0.09$). Error bars indicate ±1 SEM.
Figure 3.4. Experiment 2 Primary Methods and Results. A) Example views of the virtual environment from the participant’s perspective during the feedback phase. There were two virtual arenas: one in which the arena was bounded by a wall (Wall Arena) and one in which the arena was bounded by a marking on the ground (Mat Arena). To ensure that all objects equally obscured the edges of the arenas, the target objects in Exp. 2 were five-sided polyhedrons of the same height with images of the objects textured on the polyhedron’s sides. 

B) Average distance error in virtual units (VU) in each arena, plotted separately for the OPA (dark colors) and Vertex (light colors) sessions. Stimulation to the right OPA impaired performance in the Wall Arena, but not in the Mat. Significance markers indicate the strength of the difference between OPA and Vertex for each Arena (1-tailed t-test; * p < 0.05). Error bars indicate ±1 SEM.
Figure 3.5. Experiment 2 Additional Methods and Results. 

A) The group-based right Occipital Place Area (OPA) derived from a large number (42) of subjects across several studies from our laboratory, shown in green on the average cortical surface (Julian et al., 2012). The OPA TMS target site was defined for each participant as the OPA voxel exhibiting peak scene-selectivity. Each red dot denotes an OPA target site for a single participant in Experiment 2 (mean Talairach coordinates: [35, -79, 22]).

B) In addition to the Wall and Mat Arenas, in Exp. 3 participants were also tested in the Island Arena. Data from the Island were inconclusive; see 3.3 Methods for more information.

C) Mean path length and path tortuosity during the replace phase, and mean response time during both the replace phase and feedback phase, separately for the OPA (dark colors) and Vertex (light colors) sessions for the Wall Arena (W; in blue) and Mat Arena (M; in green) (±1 SEM). Path tortuosity for each trial was computed as the path length divided by the Euclidean distance between the starting and end location of the path taken by the participant. Separate 2(arena: Wall vs. Mat) x 2(stimulation site: OPA vs. Vertex) ANOVAs revealed no significant main effects or interactions for path length, or response time during the replace or feedback phases (all F(1,11)s < 2.50, all ps > 0.14). Path tortuosity was marginally lower in the Mat than in the Wall Arena (F(1,11)=3.62, p=0.08), but critically there was no significant main effect of stimulation site or interaction (both F(1,11)s < 0.89, both ps > 0.35).
Table 3.1. Complete results of the analyses of variance performed on data from blocks 2-3 of Experiment 1. Overall performance is analyzed in the top table and influence of the landmark in the bottom table. Significant effects (p < 0.05) are indicated in bold.

<table>
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Table 3.2. Complete results of the analyses of variance performed on performance data from blocks 2-3 of Experiment 2. Significant effects ($p < 0.05$) are indicated in bold.

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CHAPTER 4: Human entorhinal cortex represents visual space using a boundary-anchored grid

In collaboration with Alex T. Keinath, Giulia Frazzetta, and Russell A. Epstein

4.1 Abstract

When participants performed a visual search task, fMRI responses in entorhinal cortex (EC) exhibited a 6-fold periodic modulation by eye movement direction. The orientation of this modulation was determined by the shape and orientation of the bounded search space. These results indicate that human EC represents visual space using grid cells anchored to environmental borders, analogous to those used to code navigable space in rodents.
4.2 Results and discussion

During spatial navigation in rodents, grid cells fire when the body of the animal occupies a hexagonal lattice of spatial locations tiling the floor of the environment (Hafting et al., 2005). Recent work with monkeys has expanded the variety of spaces that might be represented by grid cells, by demonstrating the existence of cells in EC that fire in a hexagonal lattice of positions on a screen while animals explore visual space (Killian et al., 2012). We tested whether a similar grid-like coding of visual space could be identified in humans, by using fMRI methods previously developed for identifying grid signals in humans during virtual navigation (Doeller et al., 2010). These methods are motivated by the observation that grid cell firing patterns within an individual tend to have the same orientation (Hafting et al., 2005; Doeller et al., 2010). Because of this orientation alignment, movements along versus between grid axes yield differences in the fMRI signal in human EC, resulting in 60° periodic modulation by movement direction. We reasoned that if grid cells represent visual space in humans, then we should observe a similar 60° periodic fMRI signal as a function of gaze movement direction while participants visually explore the environment.

Participants (n=36) were scanned with fMRI and had their gaze tracked while they performed an unconstrained visual search task in which they had to find a target letter ('L') among numerous distractors letters ('T's) (Fig. 4.1A). A square border surrounded the search display for half the participants (n=18) and a rectangular border surrounded the display for the other half (n=18). For each participant we split the fMRI data into halves, identified the orientation of the 60° periodic signal as a function of gaze movement direction within EC in one half of the data, and tested the reliability of this visual grid orientation in the independent second half. This analysis revealed significant reliable 6-fold modulation of the fMRI signal as a function of gaze movement direction bilaterally in EC (Fig. 4.1B; see also Fig. 4.2). This result reflects greater fMRI response when gaze movement directions were aligned with the three grid axes than misaligned (Fig. 4.1C). Conducting the same analyses for other rotational symmetries, we found no evidence of reliable 90° or 45° periodic signals across independent halves of the data in EC (Fig. 4.1D). All
gaze movement directions were sampled during the visual search task, and we detected no 6-fold biases in gaze behavior that could explain the presence of a 6-fold symmetric fMRI signal (Fig. 4.3). Thus these results are evidence of a grid representation in human EC that codes for locations in visual space, complementing previous findings of grid representations in navigable space (Doeller et al., 2010; Jacobs et al., 2013).

We next explored the coordinate system that EC uses to encode visual space. For grid cells to provide useful information about environmental locations, grid cell firing patterns must be stably anchored to the external world. In previous work examining grid cells tiling visual space in monkey EC, the head of the animal was fixed relative to the visual display, making it difficult to determine whether these cells coded locations in egocentric (head-centered) or allocentric (screen-centered) coordinates. To resolve this issue, we examined the relationship between the orientation of the grid and the geometry of the search display as defined by its borders. First, we asked whether grid orientations are reliably aligned by search display shape. When rodents explore square environments, the grid lattice aligns to ±7.5° from the cardinal axes of the borders (Krupic et al., 2015; Stensola et al., 2015) (Fig. 4.4A); we looked for a similar effect in the participants who searched square displays (Fig. 4.4B). Across these participants, the average EC visual grid orientations were significantly clustered around ±7.5° offset from the cardinal axes of the square display border (V test; v=5.18, p=0.0421; Fig. 4.4C). Moreover, of the 14/18 participants that showed significant clustering of grid angles across voxels in bilateral EC (Raleigh’s test, p<0.05 corrected for spatial smoothness), 12/14 had grid angles significantly clustered across voxels 6°-9° offset from the display borders (V test; each p<0.05, Bonferonni corrected; Fig. 4.4D; see also Fig 4.5). Interestingly, visual grid orientations for the rectangular display participants were not clustered around ±7.5° from the rectangular borders across participants (v=-2.48, p=0.796; Fig. 4.4E). Indeed, grid orientations were closer to 7.5° offset from the display borders in the square display participants than in the rectangular display participants (one-tailed t-test; t(34)=2.26, p=0.015). Because the shape of the display was the only stable
environmental feature that differed between these participants, these results confirm that visual grid orientations were affected by the geometry of the visual environment.

We next examined whether rotation of the search display would induce a corresponding rotation of the visual grid. To address this question, each participant who performed the search task with the upright rectangular search displays also completed two additional scan runs in which the displays were rotated 30° clockwise (Fig. 4.6A). If the visual grid code is anchored to the borders of the search display, then rotation of the search display should yield a corresponding 30° rotation of the visual grid orientation, as observed in navigating rodents when chamber boundaries are rotated (Krupic et al., 2015). We found that a 30° rotation of the upright-display-fit visual grid orientation significantly predicted the fMRI signal during rotated-display runs in EC (Fig. 4.6B; see also Fig. 4.7). Furthermore, rotated-display-fit visual grid orientations in bilateral EC were offset 28.33° ± 2.87° (mean angle ± s.e.m.) relative to upright-display-fit grid orientations (Fig. 4.6C). Interestingly, 6 participants showed little grid angle rotation (Fig. 4.6D). Surprisingly, these non-rotating participants were faster at finding the target letter during the rotated-display runs than the participants whose grid orientations rotated (two-tailed t-test: t(16)=3.81, p=0.002; Fig. 4.6E). Thus, although visual grids were anchored to the geometry of local visual space on average, there were individual differences in which external reference frame was selected, and these differences had consequences for search behavior.

In sum, we report the first evidence that human EC represents locations in visual space using a grid code, and that this visual grid code is stably anchored to the geometry of the visual scene. These results may illuminate a longstanding controversy over the representation of visual space. Previous evidence suggests that the mammalian visual system represents space in retinotopic coordinates (Irwin et al., 1983; Gardner et al., 2008; Golomb and Kanwisher, 2011), which are updated before each eye movement based on information about the intended direction of the upcoming saccade (Duhamel et al., 1992). Although non-retinotopic spatial codes are observed under some circumstances (Galletti et al., 1993; Snyder et al., 1998), it is often unclear whether these codes are egocentric (head-centered) or allocentric (world-centered), and
evidence for an allocentric map that represents where a viewer is looking relative to stable visual environmental cues has remained sparse (although see Rolls, 1999; Dean and Platt, 2006). The current results provide evidence for such a map, and suggest a mechanism by which it might be generated. During navigation, grid cells are thought to perform path integration by using self-motion inputs (Hafting et al., 2005; McNaughton et al., 2006b) to update allocentric representations of location that are anchored to the environmental boundaries (Krupic et al., 2015; Stensola et al., 2015). Visual grid cells may subserve a similar path integration mechanism by which an allocentric representation of the current gaze position in visual space is updated based on eye motion inputs. Consistent with this idea, eye movement information has been found throughout the hippocampal formation (Meister and Buffalo, 2016), and conjunctive grid by saccade direction cells have been found in monkey EC (Killian et al., 2015). Beyond navigation, recent work has also shown that a grid-like code is used to represent both imagined and conceptual spaces (Bellmund et al., 2016; Constantinescu et al., 2016; Horner et al., 2016). Our data add to this growing body of work by showing that grid cells may provide the mechanism by which locations in visual space are represented, thus allowing us to form durable spatial memories that are stable across eye movements.

4.2 Methods

Participants. 36 participants (14 male) took part in this experiment (mean age: 23; range: 18-32). All participants gave written consent and were paid for participating, in compliance with procedures approved by the University of Pennsylvania Internal Review Board. All had normal vision and reported to be in good health with no history of neurological disease. Data from 7 additional participants were collected but discarded before analysis of fMRI data due to poor eye tracking quality (6 because of inaccurate gaze reconstructions; one because of poor sampling of all gaze angles). Data from one additional participant was discarded due to excessive head motion during scanning (>3 mm average absolute head motion).
**Visual search task.** Participants completed a series of 6.5 min fMRI scan runs during which they performed a visual search task. Square display participants completed four runs and rectangular display participants completed six runs. During each run, participants viewed visual search displays consisting of a target letter ‘L’ surrounded distractor letters ‘T’s (letter height = 0.74°). Participants were instructed to use their eyes to search for the target, and to press a button when they found the target letter. Each trial was self-paced, and lasted an average of 7.50±0.58 seconds (mean±s.e.m.). Stimuli were presented using Matlab (2016a, The MathWorks Inc., Massachusetts) and the Psychtoolbox (Brainard, 1997) (Version 3.0.11). A pseudo-random search display was generated on each trial, such that all letters had a random orientation and location within the borders of the search display shape. Only partial overlap between the letters was permitted. Each search display had one of three possible densities ([100, 144, 169] or [81, 100, 121] letters total in the square and rectangle conditions, respectively). The search display density was randomly selected on each trial, with the constraint that each of the three possible densities was presented once before repeating. Search displays subtended a visual angle of 17.0° x 17.0° (square participants) or 11.0° x 17.0° (rectangular participants), and the search display border line thickness was 0.21°. There was a variable inter-trial interval of 2-6 seconds, randomly selected on each trial, during which participants fixated on a centrally located fixation cross. The onset of each trial was time-locked to the onset of an fMRI acquisition.

For the rectangular display participants, four scan runs consisted of upright rectangular displays, and two runs consisted of rectangular displays rotated by 30° clockwise. For these participants, the presentation order of the displays was URUURU, where U and R correspond to upright and rotated displays, respectively. This ordering ensured that any effect of display rotation could not be due to general drift across runs.

**Eye tracking methods and preprocessing.** Participant’s gaze position during scanning was monitored and recorded using a LiveTrack AV MR-compatible eye tracking camera (Cambridge Research Systems, Rochester England). The gaze position of the right eye was recorded at 30
Hz. Prior to each scan run, gaze position was calibrated using a series of nine fixation points evenly spaced between -8° and +8° in the horizontal and vertical dimensions relative to screen center. The average calibration error across all runs was 0.332° ± 0.018° (mean ± s.e.m.). In order to separate periods of gaze movements from periods of fixations, periods of gaze movement were defined by a movement-velocity-thresholding procedure, as follows. To reduce detection of gaze movements attributable to eye tracking noise, the gaze position time course was first temporally smoothed with a boxcar filter (half width = 0.185 seconds). Gaze movements were then identified based on a median split of the smoothed gaze movement instantaneous velocity. Gaze position measurements in the bottom half of gaze movement velocities were treated as no movement, as were samples during which participants blinked. Gaze movements with velocities in the upper median half tended to be long saccades relative to the size of the search displays, with an average ballistic gaze trajectory length of 1.60° ± 0.60° (mean ± standard deviation). Note that this velocity-thresholding procedure is conservative in that it excludes short gaze movements during which we would not expect to observe a strong grid-like fMRI signal, based on previous fMRI studies of human navigation (Doeller et al., 2010; Horner et al., 2016). Based on this method of classifying gaze movements, 7.1% ± 0.57% (mean ± s.e.m.) of fMRI acquisitions were classified as containing no gaze movements whatsoever, which serves as the implicit baseline relative to which fMRI signal change was measured.

**fMRI acquisition.** Scanning was performed at the Center for Functional Imaging at the University of Pennsylvania using a 3T Siemens Prisma scanner equipped with a 64-channel head coil. High-resolution T1-weighted images for anatomical localization were acquired using a 3-dimensional magnetization-prepared rapid-acquisition gradient-echo pulse sequence (repetition time [TR], 1620 ms; echo time [TE], 3.09 ms; inversion time, 950 ms; voxel size, 1x1x1 mm; matrix size, 192x256x160). T2*-weighted images sensitive to blood oxygenation level-dependent contrasts were acquired using a gradient-echo echoplanar pulse sequence (TR, 1000 ms; TE, 25 ms; flip angle 45°; voxel size, 2x2x2 mm; field of view, 192; matrix size, 96x96x78; multiband acceleration
factor of 4). Ten additional fMRI volumes were also collected at the start of each scan run that were excluded from data analysis to account for signal steady-state transition. Visual stimuli were displayed at the rear bore face on an InVivo SensaVue Flat Panel Screen at 1920 × 1080 pixel resolution (diag = 80.0 cm, w × h = 69.7 × 39.2 cm). Participants viewed the stimuli through a mirror attached to the head coil. Behavioral responses were collected using a fiber-optic button box.

**fMRI analysis – preprocessing.** FMRI data analysis was carried out using FSL FEAT (FMRIB's Software Library, version 6.00, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). The following standard data preprocessing was performed: motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). For second-level group analyses, EPI images were registered to the high-resolution anatomical image using boundary-based reconstruction and then normalized into standard space (MNI305) using non-linear registration. All data normalization was performed using Freesurfer (v5.3.0, [http://surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)).

**fMRI analysis – Identifying grid-like coding of visual space.** We performed a split-half analysis to estimate the orientation of the visual grid code during periods of gaze movement, following procedures used previously to identify grid-like codes during virtual navigation (Doeller et al., 2010; Kunz et al., 2015; Horner et al., 2016; Stangl et al., 2017). Data were first split into halves by run (runs [2,4] and [1,3] for square participants; runs [1,4] and [3,6] for rectangle participants, so that only the upright rectangle runs were used to identify grid-like coding in this initial analysis). For each half of the data, we identified the angular orientation of the putative visual grid axes in each participant’s bilateral EC. The grid orientation thus obtained was then subsequently used to predict a grid signal during the other independent half of the runs.
To fit the orientation of the 6-fold gaze movement direction-modulated signal within EC, we constructed a general linear model (GLM) with two parametric modulators (PMs) for periods of gaze movement. These two PMs were \( \cos(6a(t)) \) and \( \sin(6a(t)) \), where \( a(t) \) is the gaze movement direction sampled at time \( t \) (30 Hz). Each PM was down-sampled to the TR (1 Hz) by summing the values of the PM within each TR. The weights (\( b_1 \) and \( b_2 \)) on these PMs were fitted to the fMRI time series for each voxel within the anatomically defined bilateral EC ROI. This EC ROI was constructed uniquely for each participant based on the automatic anatomical parcellation of the EC derived from FreeSurfer structural reconstruction. We then calculated the orientation of the 6-fold gaze movement direction-modulation from the mean weights across all voxels in the EC ROI, as \( \phi = \frac{\arctan(<b_2>/<b_1>)}{6} \), separately for each run. Note that because of the 6-fold symmetry, the possible range of \( \phi \) is between 0° and 60°. Finally we computed the circular average orientation across runs for each separate half of the data. Grid orientations were quantitatively similar if we averaged the beta weights voxel-wise across runs before calculating the orientation instead of averaging the orientations across runs (circular correlation across participants: \( c=0.84, p<10^{-5} \)).

To test whether the fit orientations predicted the analogous 6-fold periodic signal in the other independent half of the data, we constructed a GLM with a PM modeling the effect of gaze movement direction on the fMRI signal. The value of this PM at each timepoint was the cosine of gaze movement direction at that timepoint aligned to the orientation predicted by the first half of the data, \( \cos(6(a(t)-\phi)) \), where \( a(t) \) is the gaze movement direction sampled at time \( t \) (30 Hz). This PM was down sampled to the TR by summing the values of the PM within each TR. Each beta from this analysis reflects the extent of reliable split-half \( \phi \)-oriented 6-fold gaze movement direction-modulated fMRI signal (which we call “orientation consistency”). The beta weights for this PM were averaged across all scan runs within each participant. The group-level test of the significance of these weights was small-volume FWE-corrected (SVC) within a group-level bilateral EC ROI, which was defined as the union of all individual-participant anatomically-defined EC ROIs projected into MNI space. To confirm that the gaze movement direction-modulated
signal in EC exhibited a specifically 60° periodicity, we conducted this same split-half analysis for 90° (i.e., 4-fold) and 45° (i.e., 8-fold) periodicities.

Analyses were performed in FSL using FILM with local autocorrelation correction (Woolrich et al., 2001). Included in all GLMs was a binary boxcar regressor of no interest corresponding to periods of visual search and its temporal derivative, as well as six nuisance PMs to account for head motion-related artifacts. All regressors were convolved with double gamma hemodynamic response function and filtered by the same high pass filter as the fMRI data before entry into the GLM.

For all region of interest analyses of fMRI responses (Figures 4.1 and 4.2), we used t-tests to compare percent signal change or orientation consistency values to baseline. The distributions of fMRI responses and orientation consistency values met normality assumptions for each test (Lilliefors test, all ps>0.05). All t-tests were evaluated against a one-tailed p<0.05 level of significance in the direction of the stated prediction, unless otherwise specified.

**fMRI analysis – reliable offset of the grid-like representation orientation from the search display shape.** To test whether grid orientations consistently cluster around an offset of ±7.5° from the cardinal axes of the search display borders across participants, we first computed the average of the grid orientations across all EC voxels and runs within each participant. We then folded the grid orientations of all participants by $\varphi \mod 15^\circ$, which aligns all hypothesis-consistent alignments to $7.5^\circ$ in a circular $0^\circ$ to $15^\circ$ space. Next we performed a V-test for nonuniformity centered around $7.5^\circ$. The V-test is similar to Rayleigh’s test for circular uniformity with the difference that under the alternative hypothesis the distribution is non-uniform centered at a particular hypothesized angle (in this case, $7.5^\circ$) (Zar, 1999; Berens, 2009).

To test whether individual participants showed grid orientations clustered around $7.5^\circ$ offset from cardinal axes, we first evaluated whether each participant showed orientation clustering across EC voxels around any angle. To do so, we averaged the grid angle derived from each voxel across runs, yielding a distribution of voxel-wise grid orientations. Next we tested
these voxel-wise grid orientations for non-uniformity using Rayleigh’s test for circular data. Note that because grid orientations were averaged voxel-wise across fMRI runs for this analysis, significant orientation clustering also requires temporal stability across runs of the grid orientation across voxels. This identified participants who had significant nonuniformity, i.e. orientation clustering, of grid angles in EC (p<0.05, accounting for spatial smoothing). Finally, we tested whether the voxel-wise grid orientations in participants with significant clustering were specifically clustered around 6.0°-9.0° degrees in 0.5° increments (via folding and V-test, as described above; p-values were Bonferonni corrected for the seven grid angles tested).

**fMRI analysis – rotation of the grid-like representation orientation with rotation of the search display.** To test whether the visual grid orientations of rectangular-display participants rotated in concert with the rotated displays, we first computed the circular average of the grid orientation derived from each upright-display run. Next we rotated this average grid orientation, $\varphi$, by 30° and used this rotated orientation to predict the fMRI signal during rotated-display runs with a GLM. Specifically, a single PM to was used to model the effect of gaze movement direction on the fMRI signal during the rotated rectangle runs: a cosine of gaze movement angle aligned to the 30° rotated grid orientation, $\cos(6(\alpha(t)-(\varphi+30°)))$. Positive weights from this analysis indicate that the 60° periodic fMRI signal is better predicted when the orientation of the grid axes is rotated 30° than upright during rotated-display runs, whereas negative weights indicate the converse. The weights for this PM were first combined across both rotated-display runs in each participant, and then tested across participants with small-volume FWE-correction within the group-level bilateral EC ROI.

To examine the distribution of rotation effects across EC voxels, we first identified the grid orientation for each voxel during the rotated scan runs in the same fashion as we did for the upright scan runs. We then compared the distribution of grid orientations across all EC voxels when the display was upright to the distribution when the display was rotated. Specifically, for each participant, we subtracted $\varphi$ from each EC voxel’s grid orientation, separately for the upright
and rotated display runs, so that the average grid orientation across voxels were aligned relative to $\varphi$ in each participant. We then calculated the distribution of voxels with grid orientations occurring from $0^\circ$-60° in 2° increments separately for the upright and rotated scan runs, and subtracted the upright distribution from the rotated distribution. If grid orientations across voxels rotate in concert with rotation of the search display, then there should be a higher percentage of voxels with grid angles around $\varphi$+30° when the display is rotated than upright.
Figure 4.1. Visual grid-like representation in human entorhinal cortex (EC). A) Left: example square visual search display (for display purposes, example display has fewer letters than actual displays and relative letter size is increased). Right: schematic of the entire scene visible during scanning. B) Reliable grid-like coding of visual space was observed in bilateral EC (p<0.05, SVC in bilateral EC; peak MNI coordinates: 40/-4/-38, peak Z=3.09). C) fMRI response in a 2mm sphere centered on the peak EC voxel from (b) for periods of gaze movement aligned to grid orientation $\phi$ (within $\pm 15^\circ$ of a $\phi$ axis) and misaligned (more than $\pm 15^\circ$ from all $\phi$ axes) (aligned: t(35)=1.95, $p=0.030$; misaligned: t(35)=-2.60, $p=0.014$, two-tailed). D) Split-half orientation consistency (beta weight) in the spherical EC voxel ROI from (c) for 90$^\circ$ and 45$^\circ$ periodicities (magnitude of 60$^\circ$ plotted for scale). Neither 90$^\circ$ nor 45$^\circ$ showed significant orientation consistency (both t(35)s<1.02, ps>0.841). Note that these null effects were not specific to the EC ROI based on the 60$^\circ$ periodicity analysis, as we saw no effect for 90$^\circ$ or 45$^\circ$ in the entire EC at p<0.05 (SVC). *p<0.05; ***; p<0.001; ns, not significant. Error bars show $\pm 1$ SEM.
Figure 4.2. Visual grid-like representations are largely specific to entorhinal cortex (EC), and are present for both display shapes. A) Sinusoidal modulation of BOLD response by gaze movement direction with 60° periodicity, shown unmasked on the inflated cortical surface at an uncorrected statistical threshold for display purposes. No voxels survived whole-brain FWE correction. B) Orientation consistency across split-halves of the data in a 2mm sphere centered on the peak EC voxel identified from the group analysis including all subjects (Fig. 1B) for 90°, 60°, and 45° periodicities separately for the square (left) and rectangle (right) display shape participants. For both groups, there was significant orientation consistency across runs for 60° periodicity (square: t(17)=2.26, p=0.019; rectangle: t(17)=2.48, p=0.012), but not 90° (square: t(17)=2.32, p=0.808; rectangle: t(17)=0.82, p=0.788) or 45° (square: t(17)=2.83, p=0.840; rectangle: t(17)=0.499, p=0.688). C) In order to confirm that the grid-like coding of visual space observed in EC was not due to a visual confound, we applied the same ROI analysis to a visual cortex ROI, which was anatomically defined for each participant as the left and right occipital poles. Not surprisingly, EVC showed a strong response during periods of visual search compared to fixation (left; colored voxels are significant when whole-brain FWE-corrected). There was no significant 60° (t(35)=1.05, p=0.151) or 45° (t(35)=1.24, p=0.111) periodic orientation consistency in this region, but there was significant 90° (t(35)=2.49, p=0.009) periodic orientation consistency (right). Indeed, there was significantly greater 90° periodic orientation consistency in EVC than in EC (t(35)=2.43, p=0.020). The presence of a reliable 90° periodic signal in EVC likely reflects the cardinal direction gaze movement bias (Fig. 4.3). * p < 0.05; ** p < 0.01; ns, not significant; Error bars show ±1 SEM.
Figure 4.3. No biases in visual behavior are confounded with grid-like coding of visual space. A) Percentage of total gaze movements by direction in individual participants (top row) and on average (bottom row). Each possible gaze movement direction was sampled both within individual participants, and on average. B) Relative proportion of gaze movement directions modulo 90°, 60°, and 45°. Gaze tended to move disproportionately along the cardinal directions defined by the search display shape, as reflected by the peak centered around 0° in modulo 90° space. Critically, however, there was no 60° periodic bias in gaze movement directions that would be confounded with the presence of a specifically 60° periodic fMRI signal dependent on gaze movement direction. C) Participants searched all locations in the search displays in both the square and rectangle search displays. Gaze sampling maps during gaze movement from all fMRI scan runs are shown, with the region around the central fixation cross that was presented between trials removed. D) Within each TR, gaze tended to move in only a single direction; $\alpha$ denotes the modal gaze movement direction within a given TR. E) Difference in length of time with gaze movements aligned to each participant's average EC grid orientation $\phi$ (within ±15° a $\phi$ axis) versus misaligned (more than ± 15° from all $\phi$ axes), separately for the square and rectangular display participants. There were significantly more gaze movements along misaligned than aligned directions for the square display participants (2-tailed t-test; $t(17)=2.99, p=0.008$), though the magnitude of the difference was small (mean ± s.e.m.: 8.83 ± 2.95 seconds on average per scan run). There were no more gaze movements aligned than misaligned in the rectangular display participants ($t(17)=0.95, p=0.360$). F) Difference in gaze movement speed that passed the gaze motion speed threshold aligned versus misaligned to each individual participant's average grid orientation separately for the square and rectangular display participants. Gaze movement speed did not differ between aligned and misaligned for either the square or rectangle display subjects (square: $t(17)=0.44, p=0.666$; rectangle: $t(17)=0.55, p=0.588$). ** $p < 0.01$; Error bars show ±1 SEM.
Figure 4.4. Visual grid orientation is anchored to the search display geometry. A) The grid orientations of rodents navigating through square environments align to an offset of 7.5° perpendicular to an environment wall (example cell shown is adapted from ref. [6]). B) We tested whether the visual grid orientation \( \phi \) was similarly offset 7.5° from the square display borders. Specifically, because the possible range of \( \phi \) is between 0°-60°, we examined whether grid orientations cluster around 4 possible angles, each 7.5° from one of the two cardinal axes of the display borders. C) Grid orientations of the square display participants. Left: average grid angle in each participant (blue squares); Middle: histogram of average grid orientations across participants modulo 15°; Right: average percentage of grid orientations modulo 15° across all bilateral EC voxels. D) Polar histograms of all EC voxel grid orientations for two exemplary square display participants. Note clustering of grid orientations around ±7.5° from the display border (V test; both \( v>180.42, p<10^{-9} \)). E) Grid orientations of the rectangular display participants (red rectangles), organized as in (c). Error bars show ±1 SEM.
Figure 4.5. Clustering of grid orientations in entorhinal cortex (EC) within each participant. Polar histograms show grid orientations (on the range 0º-60º) for all voxels in the individual subject EC ROIs, separately for each participant (one histogram per participant) for the square display (blue) and rectangular display (red) participants. Each histogram radius is scaled to the maximum number of voxels in a given bin for that histogram (range of max across subjects: 8% - 51% of total EC voxels). Grid orientations were significantly clustered in 28/36 participants (Rayleigh's test, accounting for spatial smoothing, on each participant; * p < 0.05). For the square participants, we also tested whether grid orientations were clustered 6º-9º from the search display borders (V test for clustering around 6º-9º in 0.5º increments, Bonferroni corrected for 7 orientation tested; boxed:* p<0.05).
Figure 4.6. Visual grid orientation rotates in concert with rotation of the search display. A) For the rectangular display participants, the search displays were rotated 30° clockwise during two scan runs. B) For the rotated-display runs, we tested whether a 30° rotation of the grid orientation $\phi$ identified in the upright-display runs ($\phi+30^\circ$) better predicted the fMRI signal than no rotation of $\phi$. In left EC, we found significantly greater 60° periodic sinusoidal modulation of the fMRI signal when gaze movements were aligned to $\phi+30^\circ$ than no rotation of $\phi$ (SVC in bilateral EC, p<0.05; peak MNI coordinates: -24/-5/-44, peak Z score = 3.32). No right hemisphere EC voxels survived SVC, and no EC voxels showed greater modulation aligned to $\phi$ than $\phi+30^\circ$. C) The percent difference in the distributions of grid orientations across all bilateral EC voxels during the rotated-display runs minus upright-display runs in each participant (bottom row) and on average (top row). There were more voxels with grid orientations around $\phi+30^\circ$ ($\pm 15^\circ$) when the display was rotated than upright ($t(17)=3.95$, p<0.001). D) Difference in average grid angles derived from upright-display runs versus rotated-display runs in each participant. E) Comparison in response latency between subjects whose grid angles rotated with the display (Rot; dark rectangles in (d); $>15^\circ$ absolute upright vs. rotated difference) and those subjects whose grid angles remained fixed relative to an alternate reference frame (Nonrot; light rectangles in (d); $<15^\circ$ absolute difference). **p<0.01; Error bars show ±1 SEM.
Figure 4.7. Visual grid orientation $\phi$ rotates in concert with rotation of the search display. For the rotated-display-runs, we found significantly greater 60° periodic sinusoidal modulation of the BOLD response when gaze movements were aligned to $\phi+30^\circ$ than no rotation of $\phi$, shown unmasked on the inflated cortical surface at an uncorrected statistical threshold for display purposes. No voxels survived whole-brain FWE correction.
The aim of this thesis was to explore how the mammalian brain anchors spatial representations to the visual world. In a series of behavioral, TMS, and neuroimaging experiments with rodents and humans, the present work provides experimental support for two broad conclusions. First, the ability to re-anchor the cognitive map of navigational space to the world after becoming lost relies on multiple interacting cognitive and neural systems (Chapters 1-3). Previous psychological and ethological research has revealed the kinds of cues that guide mammalian reorientation behavior, demonstrating the particular importance of environmental boundaries. On the other hand, extensive electrophysiological research has uncovered separate components of the instantiation of the cognitive map, including place, grid, HD, and border cells. The present work begins to bridge these historically separate research programs. In Chapter 2, we found evidence for dissociable cognitive systems in mice for context recognition and heading retrieval, consistent with earlier electrophysiological studies that suggested that these processes have distinct neural substrates. In Chapter 3, we showed that the human OPA is causally and selectively involved in perception of boundaries during navigation, thus revealing the neural basis of a cognitive function hypothesized based on reorientation behavior. By theoretically bridging multiple levels of explanation, both within- and across-species, this work provides an important step toward developing a convergent model of how the brain solves the fundamental navigational problem of spatial reorientation.

Second, although there are striking similarities in the processes that mediate navigation across mammalian species, compared to other species, human and non-human primates are uniquely visual creatures (Ekstrom, 2015). For example, unlike primates, the rodent retina lacks a fovea and the majority of photoreceptors are rods specialized for vision under low light conditions, which together results in low visual acuity (Jeon et al., 1998). To compensate for this low visual acuity, rodents rely on head movements rather than eye movements to explore visual space (Huberman and Niell, 2011). Because of the relative importance of vision in primates, it is
possible that the mechanisms involved in anchoring the cognitive map during navigation are also co-opted in primates for visual exploration. We provided support for this conclusion in Chapter 4, by showing that human entorhinal cortex supports a grid-like map representation of visual space, and this visual grid code obeys some of the same principles of boundary-anchoring previously observed in rodent grid cells representing navigational space.

The existence of a cognitive map of visual space that exhibits similar anchoring principles as the mental map of navigational space raises a number of outstanding questions for future research to resolve. Of utmost importance is determining if the same grid cells that represent navigational space also represent visual space, or if distinct entorhinal populations mediate these two different domains. Second, what role might the heading retrieval and context recognition systems play in anchoring the cognitive map of visual space? Context recognition has a clear visual analogue: the background content of a visible scene, or visual context, is known to guide eye movements so that observers fixate the most important aspects of the scene (Chun, 2000). Does the same neural system mediating context recognition during navigation also represent visual context for the purpose of guiding eye movements? It is less clear what function the heading retrieval system serves in the visual domain. There are cells in the medial entorhinal cortex that code gaze movement direction (Killian et al., 2015), but such cells should not be treated as homologous to HD cells, which code the facing direction of the animal’s head and not movement direction of the animal. Third, is the OPA also involved in perceiving the boundaries of visual space? This question could be addressed using an analogous paradigm as that used in Chapter 3, but for visual rather than navigational space. More broadly, though it is known that the borders of a stimulus display constrain visual search behavior (Rosenholtz, 2001; Haimson et al., 2004; May and Zhaoping, 2009), future work should determine what constitutes boundaries of visual space in the natural environment.

Characterizing the mechanisms involved in anchoring the cognitive map is not only important for understanding navigation and vision in the typical mammalian brain, but is also relevant for understanding the neurobiological basis of deficits found in disease. Most notably,
patients with Alzheimer's disease (AD) become lost even in familiar surroundings. Navigation impairments can be detected before the development of the full AD dementia syndrome, in the stage of mild cognitive impairment (MCI) (Vlček and Laczó, 2014), and even in typical older adults (Gazova et al., 2013). As a result, older adults tend to rely to a greater extent on navigational strategies (e.g., route-following) that do not require use of a cognitive map, even when the use of such strategies is maladaptive (Wiener et al., 2013). It is possible that the fidelity of cognitive maps in these individuals is degraded, or that their cognitive maps become unmoored from the external world more easily than in a typical younger population. Pathological changes in AD and MCI occur in some of the brain regions mediating our ability to anchor the cognitive map to the world (Vlček and Laczó, 2014). These changes initially occur in the hippocampus and entorhinal cortex, further spread throughout the parahippocampal cortex in MCI and preclinical AD, and subsequently spread to the temporal and parietal lobes by the time of AD (Braak and Braak, 1995; Petersen et al., 2006). In addition to navigation deficits, medial temporal lobe damage also impairs performance on visuospatial memory tasks and causes atypical looking behavior (Chun and Phelps, 1999; Ryan et al., 2000), suggesting that an intact cognitive mapping system is also critical for remembering locations in visual space as well. Understanding the mechanisms by which the cognitive map can become un-tethered from the visual world could lead to more principled hypotheses about the neural etiology of the behavioral impairments in disease, better predictions about the onset of emergence of these impairments, and to therapeutic advances.

As a coda to this conclusion, it is worth noting that the cognitive mapping system may also support representations beyond those used for navigation or vision (Schiller et al., 2015). Indeed, although this idea has long been hypothesized (Tolman, 1948; O'keefe and Nadel, 1978), recent theoretical reviews have begun to describe in more concrete terms how the hippocampal formation in humans and rodents could mediate information processing in domains that are not explicitly spatial. For example, Buzsáki and Moser (2013) characterize how the same neural machinery that supports real-world navigation could mediate memory function broadly as a form
of navigation in mental space (see also, Milivojevic and Doeller, 2013). Recent experimental work also provides evidence for non-spatial coding by the cognitive mapping algorithm, including auditory (Aronov et al., 2017, 2017), social (Tavares et al., 2015) and conceptual (Constantinescu et al., 2016) spaces. Constantinescu and colleagues (2016), for instance, had human participants learn an abstract “space” consisting of morphed stimuli (birds that could vary along neck or leg length, or both). Using a similar methodological approach as we did here in Chapter 4, the authors found that human entorhinal cortex shows a 6-fold periodic modulation of the fMRI signal as a function of “movement” through a sequence of bird-space stimuli, thus providing evidence for the existence of grid cell coding of conceptual spaces.

It is possible that any knowledge structure that can defined based on the relative distances and angles between elements in that representational space relies on the same mental cartography system used for navigation and vision (Balkenius and Gärdenfors, 2016). An important test of whether such mental maps are used as neural tools for organizing information broadly is whether map-like representations in these domains that are not explicitly spatial obey similar anchoring principles elucidated here for navigation and vision. For example, you may need to reorient your representation of the social network among your peers in light of changes in friendships and affiliations. Or in the domain of conceptual knowledge, each time you access a conceptual space it must be retrieved from memory – akin to the mnemonic reorientation performed during a JRD task. The existence of similar boundary-anchoring principles in vision and navigation found here suggests that similar computations may mediate mental maps in these non-spatial domains as well. It is currently unclear what constitutes a “boundary” in these non-spatial domains, but the fact that boundaries may be important in navigation because they are particularly stable cues suggests that “boundary” anchoring in these broader domains may reflect anchoring to stable reference points in the representational space. For example, the mental map of conceptual spaces may be re-anchored during memory retrieval relative to prototype or exemplar concepts (Margolis and Laurence, 1999). If so, as Tolman (1948) presaged, the
mechanisms that support the cognitive map serve as a fundamental psychological operation that organizes experience and flexibly guides purposeful behavior in general.
APPENDIX

Appendix 1. Factors influencing the use of non-geometric features for reorientation

1.1 Cognitive Mechanisms

Despite the importance of geometric cues for reorientation, non-geometric and geometric information are combined for reorientation under some circumstances. Consideration of the circumstances under which features are used for spatial reorientation provides a useful handle for linking the computations performed by particular neural systems with the spatial behaviors that such systems might support.

1. Development. Controlled-rearing experiments with chicks, mice, and fish have shown that reorientation by geometry does not depend on experience with layouts having a particular geometric structure (Brown et al., 2007; Chiandetti and Vallortigara, 2008; Twyman et al., 2013). Animals raised in circular (mice and chicks) or spherical (fish) environments reoriented just as well by the shape of a rectangular chamber as animals who were raised in rectangular chambers. The ability to use geometry for reorientation does not even depend on experience with extended surface boundaries during development. Wild-caught mountain chickadees develop in feature-rich forest areas with limited access to salient geometry or extended surfaces of any type. When tested in a standard spatial reorientation task, these chickadees successfully used geometry to reorient (Gray et al., 2005). In contrast, rearing influences the use of features for reorientation. When geometry and features were placed in conflict, chicks raised in a circular environment were more likely to use featural cues over geometry, while those who were raised in rectangular environments were less likely to use the featural cues over geometry. Mountain chickadees were also more biased to use the features than wild-caught black-capped chickadees, who develop in geometry rich environments (Batty et al., 2009a). Development thus appears to influence reorientation by non-geometric features, whereas geometry is used even in the absence of development with extended surface boundaries. This suggests that the neural systems mediating
heading retrieval and localization may show an early and robust sensitivity to spatial geometry, but not features.

2. Size of the environment. Many studies have shown that environmental size plays a role in the relative salience of geometric versus featural cues during reorientation (Chiandetti et al., 2007). Learmonth and colleagues (2008) performed a spatial reorientation task with children using a larger enclosure than ones typically used to demonstrate geometric bias in children (Learmonth et al., 2008). While the space used by in early studies with children was only 4 x 6 feet (Hermer and Spelke, 1994), Learmonth et al. used a similarly proportioned space four times as large (8 x 12 feet). In the smaller space, children did not use the featural information, while in the larger space those same children used both featural and geometric information. An effect of size on encoding of features and geometry has also been observed in both chicks (Vallortigara et al., 2005; Chiandetti et al., 2007; Chiandetti and Vallortigara, 2008) and fish (Sovrano et al., 2007). The common finding is that bias to rely on geometry for spatial reorientation over features tends to decrease as environment size increases (Chiandetti et al., 2007). The importance of environmental size may be related to the fact that in larger environments the features are more distal and, in general, distal features exert more control over spatial behavior than proximal cues in a wide variety of spatial tasks (O'keefe and Nadel, 1978). However, this does not completely account for these environment size effects: restricting participants’ movement to a small part of a large room increases the propensity of children to make geometric errors, despite the cues being more distal in this case than in the standard small-chamber reorientation task (Learmonth et al., 2008).

3. Learning effects. There are three types of learning effects that influence the relative use of geometric and featural cues for reorientation. First, reorientation behavior is influenced by whether or not familiarization with the testing environment takes place oriented or disoriented. Batty and colleagues (2009) trained rats in a reorientation task in either oriented or disoriented conditions (Batty et al., 2009b). In the absence of polarizing non-geometric features, all rats,
whether trained while oriented or disoriented, used geometric cues. Further tests were then performed that placed featural and geometric cues in conflict. Rats trained in the disoriented condition preferred geometric cues to featural cues, whereas rats trained in the oriented condition showed more equal preference for featural and geometric cues. Likewise, Lourenco and Huttenlocher (2006) found that children relied purely on geometric cues to find a goal when disoriented during training, but relied on both featural and geometric cues when the environment itself had been rotated around the child instead. This suggests disorientation during familiarization with an environment increases the bias to use geometric over featural cues during testing. That said, geometry can still a particularly salient navigational cue under some circumstances even if idiothetic cues are never made unreliable. Rats learn the location of a hidden platform in a water maze faster with respect to geometric than featural cues even without disorientation (Benhamou and Poucet, 1998), and human navigators demonstrate more accurate knowledge of geometric than of featural cues during initial learning of large-scale indoor environments (Stankiewicz and Kalia, 2007).

Second, featural cues may also be used for reorientation after extended training, though results are conflicting. One previous study found that children exclusively use rectangular geometry for reorientation early in training, they subsequently integrated features and geometry after just 4-12 training trials (Learmonth et al., 2008). Similar observations have been made in rodents (Cheng, 1986; Twyman et al., 2009). On the other hand, Wang et al. (1999) tested disoriented children’s memory for locations in a square chamber with a distinctively colored wall (Wang et al., 1999). Consistent with the idea that children rely exclusively on geometry to reorient, these children searched with equal probability at all four corners in the square environment (all corners being geometrically equal). Critically, the use of the feature in the square chamber was not modulated by extended training; children that played in the chamber for half an hour before testing, or were tested in five sessions with the colored wall, failed to use the feature to reorient. Given these conflicting reports, the principles governing how much training is required to conjoin geometric and featural cues are currently unknown.
Third, recent experience with geometric and featural cues have sometimes been found to influence animals’ subsequent reliance on these different cue types in other navigational contexts (Twyman et al., 2007; Ratliff and Newcombe, 2008b). With practice using a distinctively colored wall in a triangular room, children’s use of a colored wall in a rectangular room was later improved (Twyman et al., 2007). Further, when animals are trained to find a goal in a chamber containing both featural and geometric cues and the featural cues are then altered or removed, they are then found to be impaired at locating the goal under some circumstances (Pearce et al., 2006; Wilson and Alexander, 2008; Horne and Pearce, 2009; Horne et al., 2010b; Kosaki et al., 2013). Such findings have been interpreted as indicating that featural cues are used for reorientation because initially learning position and heading with a feature overshadowed learning with respect to geometry. By contrast, other studies have found that altering or removing features does not impair a navigator’s ability to subsequently locate a goal relative to geometry (Hayward et al., 2003; Doeller and Burgess, 2008; McGregor et al., 2009). These latter studies imply that learning about heading and location relative to geometry may be independent of learning relative to features. The cause of the discrepancy between these studies currently remains unclear, though see Chapter 2.2 Discussion for one possible account.

4. Motivational state. The use of geometry for spatial reorientation is modulated motivational state (Dudchenko et al., 1997a; Martin et al., 1997; Gibson et al., 2001). In an appetitively motivated radial arm maze task in which one arm was consistently baited, disoriented rats were impaired in their ability to acquire the task relative to rats who were not disoriented. However, disoriented rats were able to learn a water version of the radial arm maze under similar training conditions (Dudchenko et al., 1997b). The water maze is stress inducing, suggesting that the effects of disorientation may interact with the motivation involved in a given task. In general, rats learn to use featural cues more quickly when they are tested under aversive conditions than when they are tested under less-aversive versions of those same tasks.

1.2 Neural mechanisms
Some of the same factors that influence whether non-boundary features guide reorientation behavior have also been shown to modulate whether the neural instantiation of the cognitive map is also reoriented by non-geometric cues. First, Dudchenko and colleagues (1997a) found that the place cell map of disoriented rats rotated in concert with rotation of cue card. Prior to recording, the animals in this study had extensive training with the same features as those used in the cylindrical chamber during recording, suggesting that initial training with non-geometric features increases the likelihood that the feature will be reorient place cell spatial representations. Likewise, if animals are initially exposed to featural cues under oriented conditions, even without extensive training experience, those features are more likely to re-anchor both place and HD cell representations following disorientation as well (Taube et al., 1990; Knierim et al., 1995).

Second, the extent to which features influence HD cell activity is related to the proximity of those features to the animal. Zugaro and colleagues (2001) recorded from HD cells in disoriented rats in a chamber consisting of three objects along the periphery of a circular platform. Preferred directions of HD cells were measured before and after the group of objects was rotated. This was repeated in the presence or absence of a cylinder enclosing the platform. When the cylindrical surface boundary was present, the cells’ preferred firing direction rotated with the objects. In the absence of the enclosure, however, the head direction representation remained fixed relative to the external room. This implies that distal cues exert more control over HD cells than proximal ones, and further shows that featural cues are more likely to be used to recover facing direction if they form part of the background geometry, as in the case of the peripheral objects surrounded by the cylinder. Salience of non-geometric cues has also been found to be an important factor for determining the extent to which features reorient HD cell representation: rotation of geometric cues tended not to override the effects of multiple stable distal featural cues in HD cells, suggesting that the hierarchy of cue preference is salience-dependent rather than absolute (Clark et al., 2012).

Together, these results suggest that the extent to which place and HD cell spatial representations are anchored by features is modulated by some of those same factors that
influence feature use for reorientation behavior, including i) the amount of experience a navigator has with those features, ii) whether or not those features were initially experienced oriented or disoriented, and iii) the proximity and salience of those features to the navigator. Whether or not the other factors that influence the use of features for reorientation behavior—such as developmental experience and motivational state—also modulate whether hippocampal map and HD cell representations are reoriented by features has not yet been examined.
Appendix 2: Functional connectivity analysis of the cortical resting-state network for cognitive map-based navigation

Participants

198 adults between ages 18-35 participated in the experiment. Data were drawn from a publically available repository that is part of the 1000 Functional Connectomes Project (fcon_1000.projects.nitrc.org). All participants were prescreened to exclude individuals with a history of significant neurologic or psychiatric conditions as well as those using psychoactive medications.

Data Acquisition and Preprocessing

MR scanning was performed on a 3T scanner. fMRI data were acquired using an asymmetric spin-echo, echo-planar sequence sensitive to BOLD contrast. All studies included whole brain coverage. Structural data (for atlas transformation) included a high-resolution sagittal, T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) scan. For complete details, see fcon_1000.projects.nitrc.org.

For the entire duration of the scans, participants simply rested in the bore with eyes open. No task was instructed. Resting-state data were preprocessed using procedures common to reduce scanner artifacts, correct for head motion, and transform the data into a standard atlas space using FSL (FMRIB's Software Library, version 6.00, www.fmrib.ox.ac.uk/fsl). These preprocessing steps included: slice time correction, rigid body correction for head motion, and normalization to a common MNI template. Data were also temporal filtered to remove constant offsets and linear trends over each run while retaining frequencies in greater than 0.01 Hz, and also spatially smoothed with a 3-mm FWHM Gaussian kernel.

Analysis

We first performed a voxel-wise functional connectivity analysis to identify the cortical network for cognitive map-based navigation. The basic procedure consisted of computing, for each
participant, the voxel-wise functional connectivity (FC) map for two seed regions: the right posterior hippocampus (HIP) or the right dorsal striatum (DS—head of the caudate). The caudate was chosen as a control region because it is known to be critical for route-based navigation (Packard and McGaugh, 1996). We then used these HIP and DS FC maps to identify regions more functionally connected to neural structures supporting cognitive map-based (i.e., HIP) than route-based (i.e., DS) navigation. To construct the FC maps, we first extracted the BOLD time series from HIP and DS. We then computed FC correlation maps for the HIP and DS. Seed regions were ~2 cm$^3$ spheres centered on MNI coordinates [10 14 0] or [27 30 -3] for DS and HIP, respectively. Correlation maps were generated using the following procedures. First, several sources of spurious variance along with their temporal derivatives were removed from each voxel’s time series by linear regression including: six parameters obtained from head motion correction, the signal averaged over the whole-brain, and the signal averaged over the lateral ventricles. In this manner, variance unlikely to be involved in spatially specific regional correlations was removed from the data. Second, we computed the Pearson correlation coefficient between each seed region’s time series and each voxel’s time series. Third, correlation maps were z-scored via Fischer transform. This resulted in two whole brain FC maps for each participant, one for HIP and one for DS.

We then performed a network analysis to examine the network structure of the cognitive map-based navigation network. We first generated a set of seed regions that are part of the cognitive map-based navigation network. To do so, we intersected the HIP-DS contrast map computed in the first analysis with the standard HarvardOxford cortical brain atlas (http://neuro.imm.dtu.dk/wiki/Harvard-Oxford_Atlas), and selected all anatomical regions in the atlas that had stronger FC with HIP than DS such that 25% of voxels in each region had stronger FC with HIP than DS (at p < 0.01, uncorrected). This resulted in a set core regions in the cognitive map-based navigation network that are not also part of the route-based navigation network. We then used these seed regions to assess the functional organization of the cognitive map-based navigation network. In particular, we constructed a FC (i.e., network edge) correlation
matrix between all pairs of seeds (network nodes). We did this using partial correlation to remove variance associated with all other seeds not in the pair. We then thresholded the correlation matrix into a binary connectivity matrix (i.e., association matrix), such that the positively correlated seed pairs (after removal of all other seed time series) are ones and the rest are zeros. Finally, we visualized the association matrix as a graph, depicting the network organization of the cognitive map-based network, and identified the possible pathways from the early visual areas to the hippocampus.

**Results**

Cortical regions found to be more strongly integrated in the HIP- than DS-networks included: superior parietal lobule, intra- and supra-calcarine cortices, posterior cingulate, the precuneous, cuneal cortex, posterior parahippocampal cortex, lingual gyrus, temporal-occipital-fusiform cortex, and superior lateral occipital. Subcortically, the thalamus was also more strongly functionally connected to HIP than DS. We next constructed a connectivity matrix from these seed regions (Figure A1.3A), such that each cell denotes the correlation between the time series in each region after removing variance associated with every other seed in the network. Second, by thresholding the connectivity matrix (p < 0.05, Bonferroni corrected for number of network nodes), we formed an association matrix describing the binary connectivity within the boundary-based network (Figure A1.3B). This association matrix was then used to construct a network graph (Figure A1.3C). The organization of the cognitive map-based navigation network, and potential pathways from the superior lateral occipital region overlapping with the occipital place area (OPA) to the hippocampus in particular, are shown in Figure A1.3D. As can be seen, there are two possible pathways from which boundary-information could be transmitted from the OPA to the hippocampus: i) through medial parietal (e.g., posterior cingulate) via the superior parietal lobule, or ii) through medial temporal regions. Notably, the scene-selective retrosplenial complex (RSC) overlaps with the posterior cingulate / precuneal region, and the parahippocampal place area (PPA) overlaps with the lingual / fusiform / parahippocampal region, and the OPA overlaps with
the superior lateral occipital region. Indeed, re-analysis of these same data replacing these anatomical regions with their respective functionally-defined regions of interest (i.e., PPA, RSC, OPA) identified in an independent group of subjects (Julian et al., 2012) reveals the same network organization.
Figure A2.1. Resting-state functional connectivity results. A) Connectivity matrix depicting functional connectivity (FC) between regions in the cognitive map-based navigation network. Regions include: 1-superior parietal lobule (SPL), 2-intracalcarine cortex, 3-posterior cingulate, 4-precuneus, 5-cuneal cortex, 6-posterior parahippocampus, 7-lingual gyrus, 8-temporal-occipital-fusiform cortex, 9-supracalcarine cortex, 10-lateral occipital, 11-hippocampus. B) Association matrix describing the binary connectivity within the cognitive map navigation network. C) Graph of the cognitive map-based navigation network. For visualization purposes, early visual cortical regions (intra- and supra-calcarine and cuneus) were excluded from this graph, and the lateral superior occipital region was replaced by “OPA”. Blue and green lines denote connectivity in the dorsal and ventral streams, respectively, and black lines denote connectivity between the two streams. Line width denotes functional connectivity strength between regions. D) Potential pathways from the OPA (white star) to the hippocampus (yellow star). Early visual areas are denoted in red. Assuming a feed-forward hierarchy, only the most direct functional connections between OPA and hippocampus are shown (i.e., connections from early visual areas to regions other than OPA are not depicted).
Appendix 3. Supplementary discussion for Chapter 2.

Supplemental Discussion 1. Two mental processes are considered dissociable if they are separately modifiable. This is established by showing that there is an experimental manipulation or treatment that affects the operation of one process but not the other. In the current experiment, the treatment is the featural cue, which has no effect on heading retrieval, but is essential for place recognition. A possible counterargument to this dissociation logic is that the feature cue might be alternatively conceptualized not as a single cue, but as two separate cues. In Experiment 1, for example, the orientation of the stripes is potentially informative about place recognition, whereas the location of the cue is potentially informative about heading retrieval. Thus, the results in this case could possibly be explained by the operation of a single mechanism mediating both place recognition and heading retrieval that happens to be sensitive to the visual appearance of features (and also chamber geometry) but insensitive to the spatial locations of features. In this view, the feature is not a single treatment that affects one process but not the other (thus demonstrating separate modifiability) but two different treatments that have unequal effects on a single underlying process. This alternative account seems less likely to explain the results of Experiment 2, as the feature cue here provides information for both tasks in virtue of its spatial location. However, even in this case the alternative account cannot be entirely dismissed, as it is possible that the mice might interpret the stripes on the long wall as being perceptually different than the stripes along the short wall. If this were the case, then one might again argue that the results are explained by a single mechanism that is sensitive to the visual appearance of features but insensitive to their spatial locations. Despite these caveats, we nevertheless believe that the most parsimonious interpretation of our results is that there are two separate systems used for reorientation when lost, one for place recognition and one for heading retrieval. Note that even stronger evidence for this claim would come from a double dissociation in which one treatment affects place recognition but not heading retrieval while a different treatment affects heading retrieval but not place recognition, but this is not what we establish here.
Supplemental Discussion 2. Consistent with the standard view (Cheng, 1986), we posit that reorientation involves the retrieval of spatial heading, in addition to identification of the environment. An alternative theory proposes that reorientation involves view matching rather than heading retrieval. In this account, the animal finds the goal location by attempting to match the current visual input to a stored representation of the visual input previously experienced at the goal location. Computational view-matching models have been shown to accurately describe reorientation behavior in single chamber environments (Sturzl et al., 2008; Sheynikhovich et al., 2009; Wystrach et al., 2011), indicating that standard reorientation behavior could be based on view matching. It is important to note, however, that these studies do not provide evidence against the idea that reorientation is based on spatial geometry—they only show that, absent other data, both theories are equally likely. More recent tests in children (Nardini et al., 2009; Lee and Spelke, 2011) and chicks (Lee et al., 2012b) that have pitted view matching against reorientation by geometry have found results that are difficult to explain in terms of view matching. In particular, these studies have found that navigators are able to solve reorientation tasks that cannot, in principle, be solved by view matching (Nardini et al., 2009) and they fail to solve some reorientation tasks that could be solved by view matching (Lee and Spelke, 2011; Lee et al., 2012b). Some of these findings are discussed in depth in a recent review from Cheng et al. (Cheng et al., 2013), in which the authors argue against view-matching as a possible account of vertebrate reorientation behavior. Nevertheless, whether rodents reorient by spatial retrieval or view matching remains an open question.

The present studies may speak to this ongoing debate in two ways. First, in the present experiments, the same cues used for place recognition were ignored for heading retrieval. Thus, at a minimum, view-matching theories would need to be revised to accommodate two sets of views, one that allows the animal to determine the identity of the chamber, and another that guides the animal to the correct location within the chamber. One possibility is that these two view systems might store views with different spatial frequency content, thus leading to differential sensitivity to the featural cue. Second, the present experiments may provide evidence against
some view-matching theories in which the stored views consist of edges (Sheynikhovich et al., 2009). The non-geometric features used in the present experiments, including in the standard one-chamber reorientation task, were horizontal or vertical black stripes containing highly salient edge information. Given that the mice ignored the visual stripes when determining the goal location within each chamber, it seems unlikely that the animals navigated within the chamber by matching edges in the current view with those in a previously experienced view.


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