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From Cells to Systems: Grids and Boundaries in Spatial Memory

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Abstract

How do we know where we are? Orientation in space is key to our daily existence as we follow familiar routes, navigate to a previous location, or just try to get home as quickly as possible. As well as being interesting in its own right, spatial cognition is also a useful model system in which to understand the neural bases of cognition and memory formation more generally. Spatial behavior offers potentially straightforward correlates of neuronal activity that can be studied similarly in adults and infants of both human and non-human animals. The neural mechanisms of spatial behavior can be realistically investigated in a well-controlled way with the aid of virtual reality technologies in humans and rodents. Virtual reality can thus help to bridge the gap between electrophysiological studies in rodents and brain imaging studies using functional magnetic resonance imaging in humans. Within this framework, this article aims to translate findings from the single cell level in rodents to understand the neural and systems level mechanisms of spatial cognition in the human brain.

Keywords

hippocampus, entorhinal cortex, space, virtual reality, fMRI

Neuronal Representations of Location and Orientation in Rodents

Place cells, pyramidal cells from regions CA1 and CA3 of the hippocampus, exhibit spatially localized activity (O'Keefe and Dostrovsky 1971). Since the initial discovery, cells with spatially modulated firing have been found in almost all areas of the hippocampus and in some surrounding areas, for example, dentate gyrus (Jung and McNaughton 1993) and medial entorhinal cortex (Quirk and others 1992; Hafting and others 2005) (see Fig. 1A). Although early work was conducted on rats, similar cells have been found in a range of other animals as diverse as bats (Ulanovsky and Moss 2007), pigeons (Bingman and others 2006), and humans (Ekstrom and others 2003). The striking quality of place cells is that they seem to provide a precise representation of an animal's position in its environment. The background firing rate of place cells is very low, effectively zero. When an animal enters the receptive field (place field) of a cell, its firing rate rapidly increases, typically to a maximum between 5 and 15 Hz (Fig. 1A). In an open environment, activity is independent of the animal's orientation (O'Keefe 1976). In essence, firing is best correlated with the position of an animal's head (Muller and Kubie 1989) and can be used to infer it (Wilson and McNaughton 1993). Interestingly, the complementary representation of orientation, independent of location, is found in the "head-direction" cells of the lateral mammillary bodies, anterior thalamus, and presubiculum (Taube 1998) (see Fig. 1A). These cells fire whenever the animal's head is pointing in a given direction, independent of the animal's location (Taube 1998; Burgess, Cacucci, and others 2005), and are also common in the deeper layers of the medial entorhinal cortex (Sargolini and others 2006).

More recently, grid cells, a third kind of spatial representation, have been identified in the medial entorhinal cortex (mEC; Hafting and others 2005). Like place cells, they show stable spatially constrained firing but with the peculiarity that each cell has multiple firing fields

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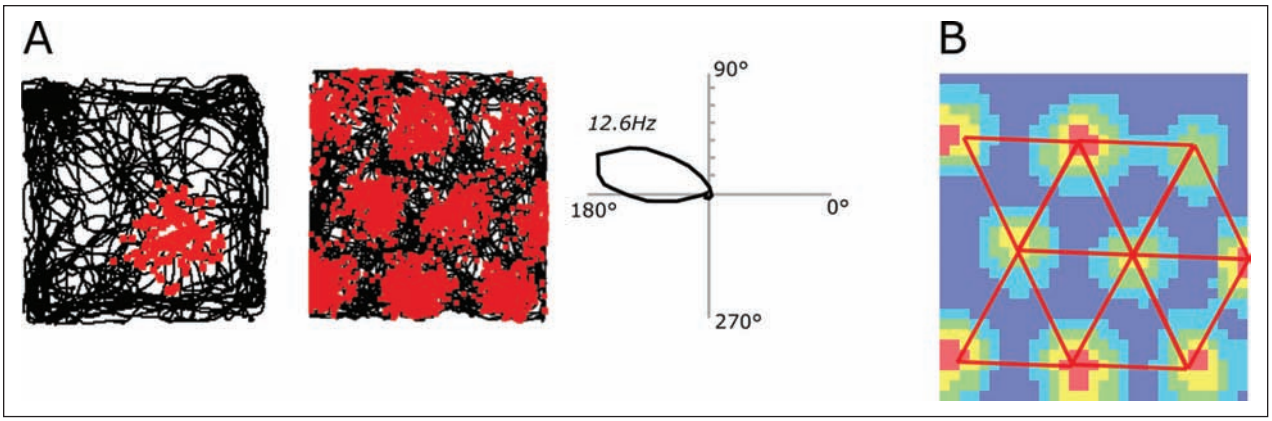

Figure 1. Neuronal representations of location and orientation in the rodent brain. (A) (left) Example of the spatially constrained firing typical of a CA1 place cell. The rat's path is denoted by the continuous black line with action potentials superimposed as red dots (8 minute trial recorded in a 70 cm × 70 cm enclosure). (middle) Similar plot for a single medial entorhinal cortex grid cell. Unlike place cells, grid cells have multiple firing fields distributed in a regular triangular lattice. (right) Polar plot showing the firing rate of a head direction cell for different orientations of the animal's head. The cell fires at a peak rate of 12.6 Hz when the animal is facing approximately northwest and is largely silent when the animal faces other directions; firing rate is not influenced by the animal's position in the environment. (B) Firing rate map constructed from raw data in the grid cell recording shown in A. Firing rate was calculated for each bin; in this case the environment was divided into approximately 30 × 30 bins. Rate is indicated by colors from "hot" to "cold" indicate firing rate as a percentage of the peak rate (dark blue 0%–20%, light blue 21%–40%, green 41%–60%, yellow 61%–80%, and red 81%–100%). The position of the grid's firing fields conforms closely to a lattice of equilateral triangles (superimposed in red).

positioned in a grid defined by the vertices of tessellated, equilateral triangles (Fig. 1). In most cases grids are remarkably regular, to the extent that they can be accurately described in terms of three variables: (1) orientation, the angle of the grid relative to an arbitrary axis; (2) spacing, the distance between adjacent grid peaks; and (3) offset, the position of the grid in two-dimensional space. Grids from neighboring locations (Hafting and others 2005), and also those farther apart (Barry and others 2007), appear to share the same orientation. Spacing, however, is topographically organized such that grids recorded from dorsal positions have a finer scale than those found more ventrally (in the rat, the peak-to-peak distance increases from approximately 25 cm to upward of several meters [Hafting and others 2005; Brun and others 2008] and does so in discontinuous jumps [Barry and others 2007]). In contrast, offset is apparently randomly distributed, even for cells recorded from the same electrode. This final point is significant as it implies that a relatively small population of grids from the same dorsoventral position will effectively tile an environment.

Grid cells, like place cells and head direction cells, have stable firing correlates, and both cell types appear to be positioned with reference to environmental cues. For example, in a circular environment devoid of directional markers, a distinct cue card attached to the wall will effectively control the orientation of the combined place, grid, and head direction cell ensemble. So, a 90-degree clockwise rotation of the cue would produce a matching rotation in the firing direction of head direction cells whereas the location of place and grid firing fields would be expected to rotate by a similar amount around the center of the environment (Taube and others 1990; Jeffery and others 1997; Hafting and others 2005). In particular, borders and barriers seem to be important in defining the locality of spatial firing. For example, geometric manipulations made to an animal's recording environment, say transforming a square arena into a rectangle, result in comparable changes in the location of place and grid fields (O'Keefe and Burgess 1996; Barry and others 2007) (see Fig. 2, A and B, and also Muller and Kubie 1987). O'Keefe and Burgess (1996) noted that the parametric changes in place field position produced by such a manipulation were consistent with place cells having receptive fields responsive to proximity of neighboring walls. This insight was formalized in the boundary vector cell model that hypothesizes the presence of a putative cell type, the boundary vector cell (BVC), tuned to the presence of boundaries at specific distances and directions (Burgess and others 2000; Hartley and others 2000; Barry and others 2006). The model describes place cell firing as the conjunctive activity of multiple BVCs and accords well with experimental data, for example, predicting the duplication of place fields when an extra barrier is inserted into an arena (Barry and others 2006) (see Fig. 2C). Beyond the firing of individual place cells, the

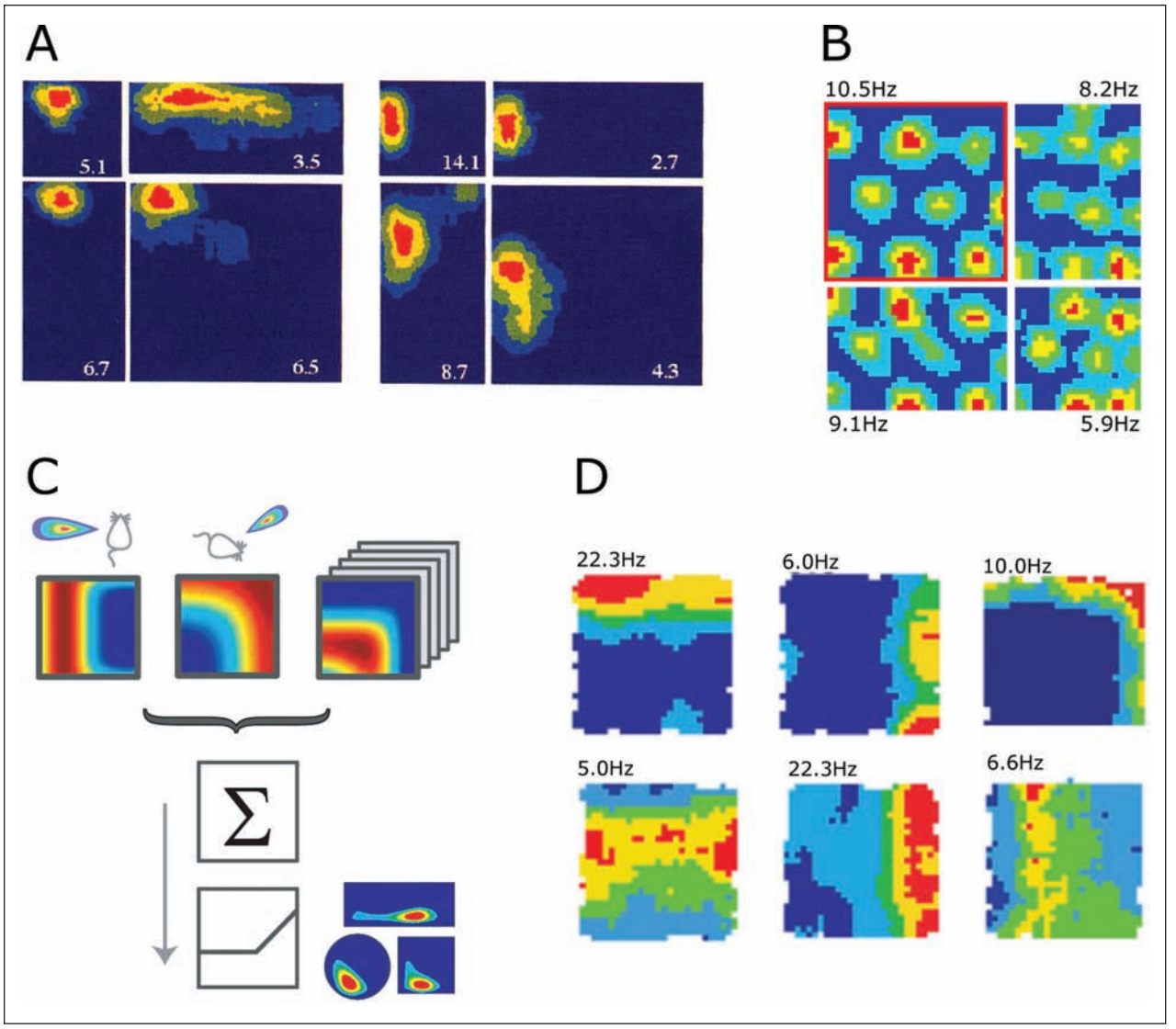

Figure 2. The importance of environmental boundaries in self-localization. (A) Rate maps for two place cells, each recorded in four rectangular arenas (small square, larger square, vertical rectangle and horizontal rectangle). Geometrically deforming the recording environment results in parametric changes in the firing fields of the cells. For example, in the case of the cell on the left, stretching the small square environment into a horizontal rectangle caused the field to stretch out along the horizontal axis. Peak firing rate in Hz is shown in white (adapted from O'Keefe and Burgess 1996). (B) Grid cell firing fields show a complementary response when subject to similar manipulation. Grids recorded in the familiar large square enclosure (outlined in red) were regular, so that fields lie in a triangular lattice. Grids recorded in the geometrically deformed probe enclosures (two rectangles and a small square) were distorted relative to the familiar grid. For example, the grid recorded in the vertical rectangle is horizontally compressed (adapted from Barry and others 2007). (C) The boundary vector cell (BVC) model postulated the existence of BVCs (top row) that exhibit spatial firing defined by the locality of barriers in an environment. For example, the left-hand cell responds maximally whenever a wall is detected a specific distance to the west of the animal. The combined input from several BVCs is sufficient to explain a place cell's firing pattern across geometric transformation of the animal's enclosure (adapted from Barry and others 2006). (D) Cells with firing characteristics similar to those predicted for BVCs have subsequently been recorded from the subiculum and mEC. Rate maps for six subicular BVCs are shown (adapted from Lever and others 2009).

model also predicts where human subjects search for a goal when the virtual environment they are exploring is geometrically deformed (Hartley and others 2004) (see below for details).

Although BVCs were initially a theoretical construct, subsequent recordings made in the mEC and subiculum found cells with spatial responses very similar to those predicted by the model (i.e., elongated firing fields that

lie along, or parallel to, the boundaries in an animal's environment; Lever and others 2009; Solstad and others 2008) (see Fig. 2*D*). The co-localization of BVCs (or border cells, as they were termed by Solstad and others 2008) and grid cells in the mEC highlights the differences between these two cell types and between the roles they have been suggested to perform. Whereas BVCs appear to be sensory-bound, encoding position relative to boundaries and barriers, grid cells have been suggested to function as a neural path integrator; enabling an animal to update its representation of location using self-motion cues (Hafting and others 2005; O'Keefe and Burgess 2005; Fuhs and Touretzky 2006; McNaughton and others 2006).

Two types of computational models describe the regular repeating firing pattern of grids as being a function of an animal's speed and direction of travel. The dual oscillator model sees grids as being an interference pattern generated between neuronal oscillators whose frequency increases above the baseline θ rhythm due to depolarization proportional to the animal's velocity (Burgess and others 2007). Indeed, electrophysiological work in slices does indicate that stellate cells in mEC layer II (i.e., putative grid cells) exhibit membrane potential oscillations (Alonso and Llinas 1989) that change in frequency in the predicted way along the dorsoventral axis of the mEC so as to mirror the change in grid scale observed along the same axis (Giocomo and others 2007). Complementary work in freely moving animals shows that the θ-band modulation of firing frequency of grid cells is also modulated by grid scale and running speed in the predicted way (Jeewajee and others 2008).

An alternative class of models sees grid firing as being generated by a recurrent network of interconnected neurons (Fuhs and Touretzky 2006; McNaughton and others 2006). In essence, the regular firing pattern of grids is seen as arising from the connectivity pattern between individual grid cells. With the appropriate connections, a mutually reinforcing "bump" of activity can be maintained and caused to track the animal's position by integrating its velocity. The two types of models may be complementary, in the following way. The membrane potential oscillations of single neurons would be too irregular to support stable spatial firing. However, connected populations of neurons can oscillate reliably (Zilli and Hasselmo 2010), consistent with the presence of a coherent θ rhythm in the local field potential (see Burgess 2008).

A common requirement for both types of models is that accumulated error in the path integrator must be corrected by sensory information about the animal's position relative to spatial cues. Without this, grid cell firing would be spatially unstable over short time periods, rather than showing the observed pattern of stable spatial firing over several days and weeks. If grid cells represent the path integrator, then it seems plausible that place cells, or possibly the entorhinal BVCs themselves, might provide the necessary sensory input to stabilize them (Burgess, Barry, and others 2005). Consistent with the former possibility, temporary silencing of place cells through local infusions of muscimol causes grid cell firing to lose spatial specificity (Hafting and others 2008).

Translation to Humans

To look at spatial representations in the human brain, we use similar paradigms as in the rodent studies by combining virtual reality (VR) technologies with whole-brain functional magnetic resonance imaging (fMRI). Participants lying in a brain scanner navigate within a virtual world, mimicking the foraging task in rodents (Fig. 3A). With fMRI, we can measure the hemodynamic consequences of the summed activity of large numbers of neurons. Thus, it is important to identify specific properties of cell firing predicting a coherent population response that would produce a macroscopic signal visible to fMRI in humans. Interestingly, virtual reality has recently been applied to rodents (Holscher and others 2005) for similar reasons to its use in humans: allowing techniques that require the head to be stationary to be applied to place cells, such as intracellular recording (Harvey and others 2009) and two-photon microscopy (Dombeck and others 2010). The ability to perform intracellular recordings verified a main prediction of the dual oscillator model of place cell firing (O'Keefe and Recce 1993; Lengyel and others 2003): that place cells have a membrane potential oscillation that increases in frequency as the cell gets depolarized when the animal enters the cell's firing field (Harvey and others 2009).

Hippocampal place cells respond to the boundaries of the environment. Inspired by the above findings in rodents, we developed a VR object location memory task (Doeller and Burgess 2008) to dissociate the influence of a local boundary from more punctuate local landmarks (which do not strongly affect place cell firing; Cressant and others 1997) (see Fig. 3A). During initial exploration, participants encountered different objects at different locations in the VR environment. At the beginning of each subsequent trial, they were cued (an image of one of the objects was shown on the screen) and then appeared in the virtual environment and had to replace the cued object in its original location in the arena (replace phase). Finally they received feedback: the object appears in its correct location and is collected again (feedback phase). Critically, landmark and boundary were moved relative to each other at the beginning of experimental blocks and half of the objects maintained a fixed location relative to the environmental boundary, whereas the other half maintained a fixed location relative to the single intramaze landmark. During the feedback phase, activity in the right

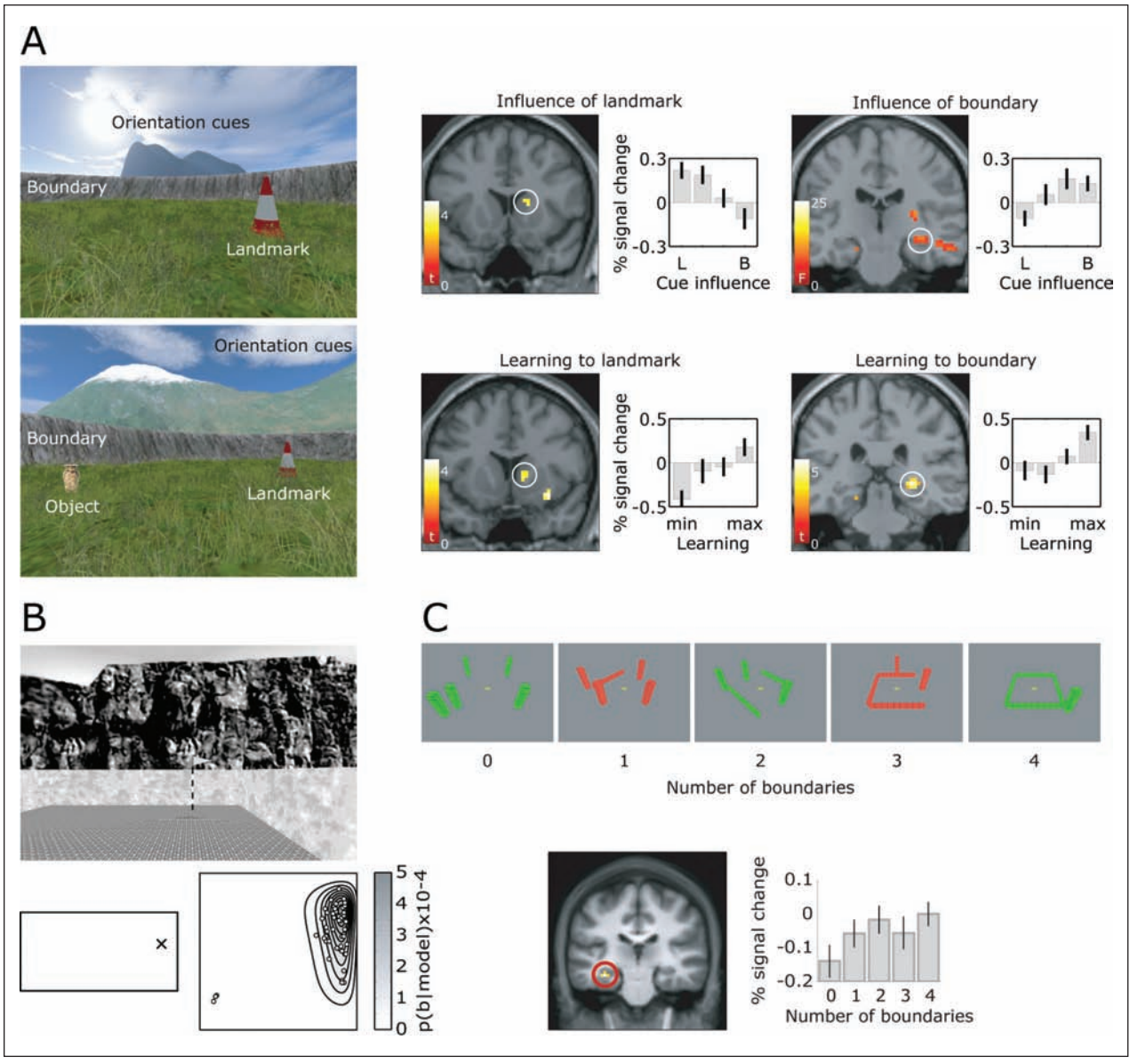

Figure 3. The human hippocampus, spatial memory, and environmental boundaries. (A) A virtual reality (VR) environment comprising a local landmark (traffic cone), a local boundary (circular wall around the arena), and distal cues (mountains) for orientation (left panels). During initial exploration, participants encountered four objects in different locations. On each subsequent trial they saw a picture of an object on a blank background and indicated its location within the arena by navigating to it from a variable start location and making a button-press response (replace phase); the object then appeared in its correct location and was collected (feedback phase). During the replace phase, dorsal striatal activity correlated with the influence of the landmark on the response, whereas hippocampal activity correlated with the influence of the boundary (top, middle, and right panels). During the feedback phase, we observed learning-related activation for landmark-based objects in the dorsal striatum and learning-related activation for boundary-based objects in the hippocampus (bottom, middle, and right panels). L, landmark, B, boundary (adapted from Doeller and others 2008). (B) Screenshot of the VR environment in the study by Hartley and others (2004; top panel) in which the location of the flag had to be remembered. When systematically changing shape and size of the arena between encoding to retrieval phases (bottom panel: encoding phase on the left; retrieval phase on the right), participants' response locations (white dots in the right plot) were well predicted by the BVC model (response density distribution) (adapted from Hartley and others 2004). (C) Examples of the scenes participants were asked to imagine (above), in which the number of boundaries (walls) varied from 0 walls to 4 walls (top panel). Activity in the hippocampus correlated with the number of boundaries in the scene during the imagination phase of the task (bottom panels) (adapted from Bird, Capponi, and others 2010).

posterior hippocampus correlated with learning locations relative to the boundary, whereas dorsal striatal activation reflected learning relative to the landmark (Fig. 3A). A similar dissociation was found during the replace phase: the influence of the boundary on response locations corresponded to activity in the hippocampus, whereas activity in the dorsal striatum reflected the influence of the landmark (Fig. 3A). This hippocampal specialization for representations of location relative to environmental boundaries is consistent with the dependence of place cell firing on boundaries in rodent experiments.

In a series of behavioral experiments (Doeller and Burgess 2008), we examined a long-standing debate about the nature of learning: whether all behavioral learning can be explained by associative reinforcement, that is, the Rescorla-Wagner law and the "reinforcement learning" derived from it (Rescorla and Wagner 1972), an idea going back to Pavlov in the 1920s (Pavlov 1927). Although Tolman expressed the contrary opinion in the 1940s (Tolman 1948), specifically pointing to spatial learning, subsequently attributed to the hippocampus in the 1970s by O'Keefe and Nadel (O'Keefe and Nadel 1978), attempts to show violations of this rule during spatial learning in both rats and humans have been inconclusive. By using the same object-location memory task as described above, we showed that under formally identical conditions, spatial learning relative to the landmark (the striatal contribution) obeys associative reinforcement (showing "overshadowing" and "blocking"), whereas learning relative to the boundary (the hippocampal contribution) does not—being purely incidental and showing neither overshadowing nor blocking. With these studies, we provided evidence that hippocampus-dependent learning relative to the boundary is fundamentally inconsistent with reinforcement learning. This is supported by a recent report that place cell firing is not susceptible to blocking (Barry and Muller 2011) and suggests that learning from repeated experience does not necessarily occur via a single prediction error signal. Our results also provide a clear identification of the nature of the learning mechanism used by the hippocampus.

Further evidence for the importance of the boundary of an environment to spatial memory has been provided by a behavioral study (Hartley and others 2004). Participants in this experiment had to encode an object position in a rectangular VR environment and—after a brief delay—had to mark the location where the object had been. Following the aforementioned place cell study (O'Keefe and Burgess 1996), the shape and the size of the VR arena was systematically changed between encoding and retrieval phase. Consistent with the BVC model (Hartley and others 2000), systematic distortions to the boundaries caused biases in object location memory that mimic distortions of the firing pattern of hippocampal place cells (Fig. 3B).

The hippocampus has been implicated not only in spatial navigation and memory but also in imagining fictional events (Schacter and others 2007; Hassabis and others 2007). The firing of place cells in rodents (O'Keefe and Burgess 1996) and the activation of the hippocampus in humans (Doeller and others 2008) point to the importance of environmental boundaries in spatial memory. In addition, computational modeling indicates that the place cell–boundary vector cell network should be able to generate imagery for spatial scenes, in concert with a wider temporoparietal network (Burgess and others 2001; Byrne and others 2007; Bird and Burgess 2008). To investigate the hippocampal role in mental imagery in more detail, we performed an fMRI study (Bird, Capponi, and others 2010) in which participants were presented with aerial views of simple virtual scenes and were required to imagine standing within the environments. We systematically varied the number of enclosing boundaries in the imagined scenes (Fig. 3C). Hippocampal activity during imagination increased with the number of boundaries, an effect being independent of scene complexity and task difficulty. These results provide a mechanistic explanation for the role of the human hippocampus in constructing spatially coherent mental images by representing the locations of the environmental boundaries surrounding our viewpoint.

The crucial role played by the hippocampus in both spatial navigation and episodic memory has prompted much speculation regarding underlying neural representations common to both functions (see Barry and Doeller 2010 for discussion), with two leading contenders being spatial context and sequential associations. In a recent study (Igloi and others 2010), we used a new virtual reality navigation task, the starmaze, mimicking a task developed for mice (Rondi-Reig and others 2006), to dissociate these two types of representation in humans. The starmaze consists of a central pentagonal ring, five radiating alleys, and surrounding environmental cues (Fig. 4A). During learning, participants had to follow a specific path to navigate to a goal location. In probe trials, which were not distinguished from training trials in the instructions, participants had to find the goal from different departure points, which allowed us to dissociate the use of either type of representation according to the path chosen by the participant (i.e., going to the same environment location as in training trials or reproducing the same sequence of turns as in training trials). We observed a lateralized hippocampal involvement during the initial alley of the probe trials (before the first choice point). The sequential egocentric representation (sequences of body turns) corresponds to activation of the left hippocampus, whereas allocentric spatial representations (of places relative to environmental cues) correspond to activation of the right hippocampus (Fig. 4B). Our results show that rather than providing a

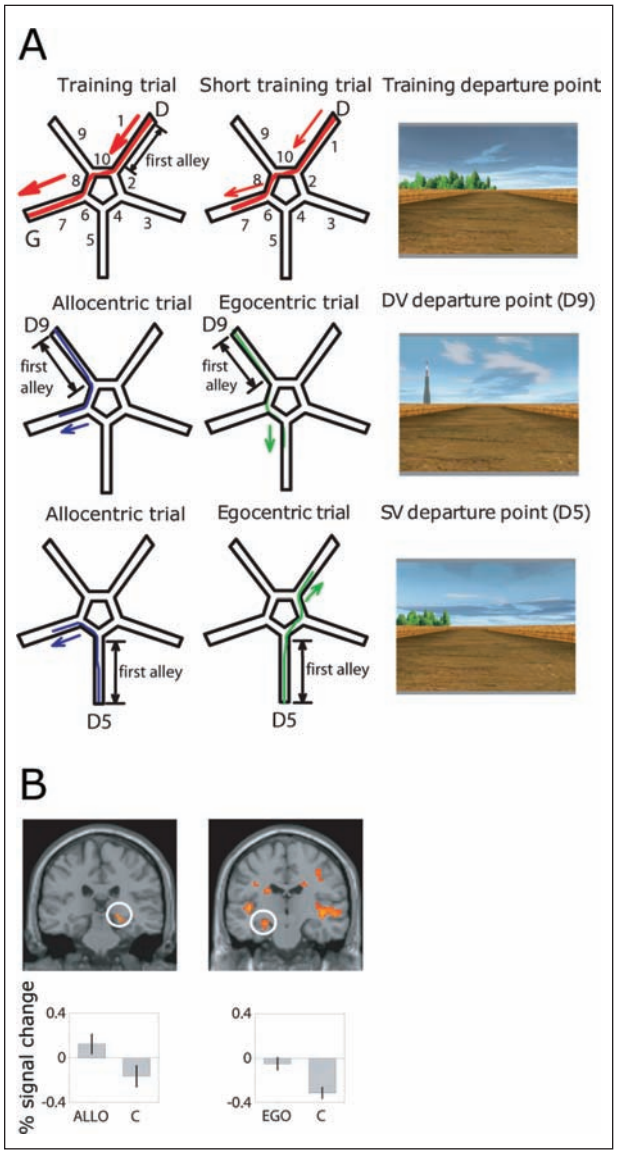

Figure 4. Place and sequence memories in the human hippocampus. (A) Schematics (left and middle panels) and snapshots from the departure points (right panels) of the starmaze task. During training (top row), participants navigate to a goal location (path indicated by the red line). During probe trials, participants start from two new departure points (middle and bottom row). Paths taken by participants using either an allocentric representation (navigating to the same environmental location as during training) or an egocentric representation (following the same sequence of body turn as during training) are illustrated by blue and green lines, respectively. (B) During the first path segment in probe trials, allocentric responses (ALLO) correspond to right hippocampal activation (left panel), whereas egocentric responses (EGO) were associated with left hippocampal activation (right panel), relative to control trials (C). Adapted from Igloi and others (2010).

single common function, the two hippocampi provide complementary representations for navigation, both of which likely contribute to different aspects of episodic memory. This also showed that human hippocampal activity can predict the use of a specific spatial representation before it is expressed in behavior. These results are consistent with the effects of disrupting hippocampal functioning in mice (Rondi-Reig and others 2006) and observations that place cell firing can reflect the animal's current trajectory (Frank and others 2000; Wood and others 2000) and potential future trajectories (Diba and Buzsaki 2007; Foster and Wilson 2006).

The discovery of entorhinal grid cells in rodents (Fig. 1) by the Moser group is one of the most exciting neuroscientific findings in recent years (Hafting and others 2005). These cells provide a strikingly periodic representation of self-location that is suggestive of very specific computational mechanisms; however, their existence in humans and distribution throughout the brain are unknown. To investigate whether similar neural mechanisms might exist in the human brain, we combined single unit recordings of grid cells in freely moving rats with whole-brain fMRI in humans navigating within virtual environments (Doeller and others 2010). Although the firing fields of different cells are shifted relative to each other, the overall orientation of the grid-like pattern is constant across cells (Hafting and others 2005; Barry and others 2007). Together with the novel finding that the firing directions of directionally modulated grid cells (Sargolini and others 2006) are aligned with the grid (Doeller and others 2010), this would predict a systematic difference of activity between runs aligned and misaligned to the grid (Fig. 5A).

We found fMRI activation and adaptation showing a 6-fold rotational symmetry in running direction in entorhinal cortex (Fig. 5B)—and surprisingly in a wider network of regions usually associated with autobiographical memory (Fig. 5C). Consistent with grid cell firing in rodents, this effect was specific to a 60-degree periodicity (rather than a 45- or 90-degree periodicity) and was speed dependent, being stronger for fast than slow runs (the spatial organization of grid cell firing [Doeller and others 2010] and the firing rate [Sargolini and others 2006] is speed dependent). Furthermore, the coherence of the directional signal across entorhinal cortex correlated with spatial memory performance, suggesting that this specific type of neural representation of space might be important for memory. The occurrence of this signal throughout the network of areas associated with autobiographical memory suggests that it might play a more general role in memory, perhaps by encoding temporal as well as spatial context (Hasselmo 2009).

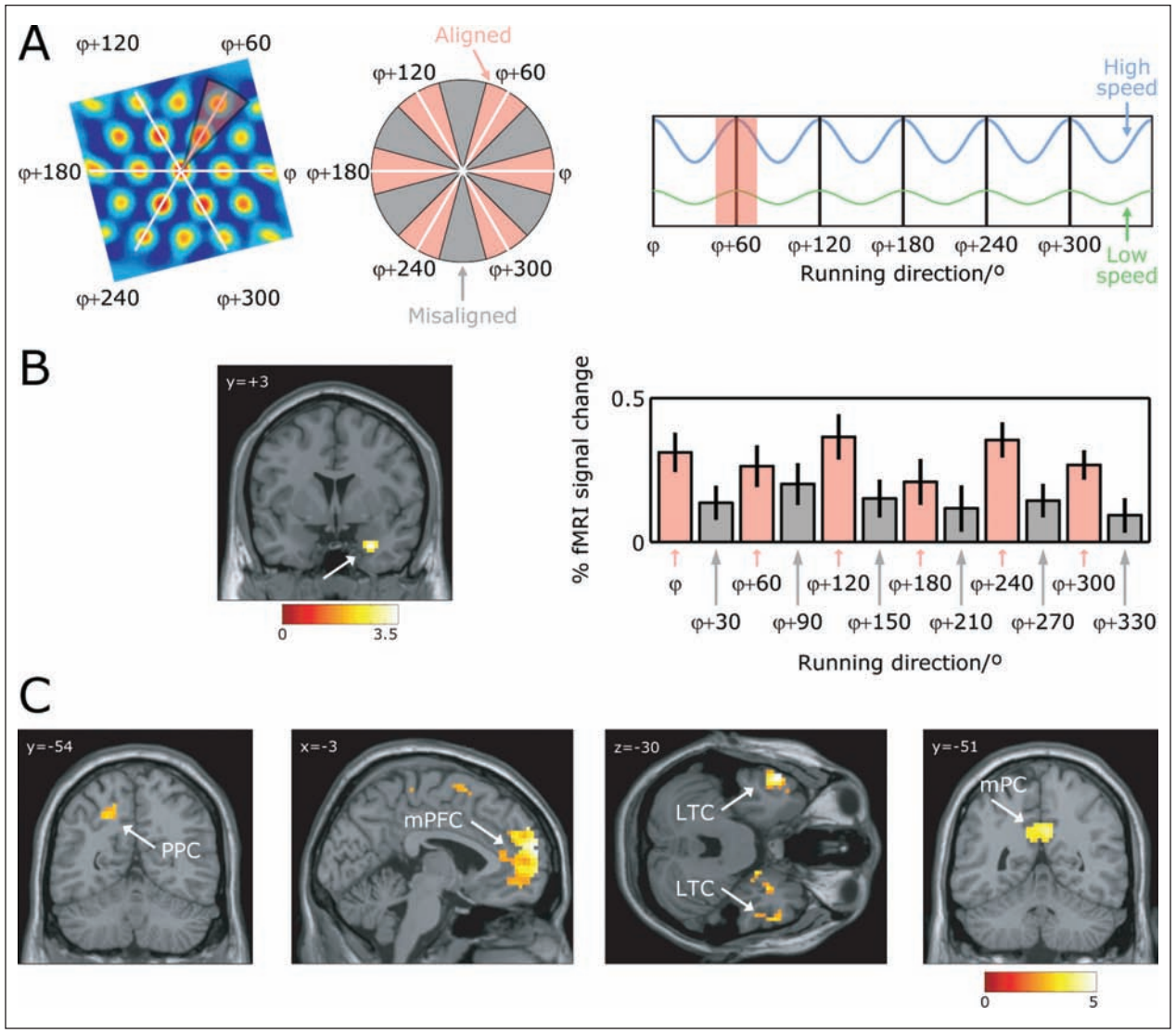

Figure 5. Grid-cell like representations in the human brain. (A) Based on the common grid orientation of different grid cells (here indicated by white lines overlaid on a spatial autocorrelogram of a typical grid cell; left panel) and the alignment of firing directions of directionally modulated grid cells with the grid, we predicted a systematic difference of activity between runs aligned versus misaligned to the grid (illustrated by red vs. gray sectors in the middle panel), that is, showing a 6-fold rotational symmetry (right panel) as a function of running direction. Given the speed modulation of grid cell firing, this effect should be stronger for fast (blue) than for slow runs (green line; right panel). FMRI activity in entorhinal cortex (B) and adaptation in a network of regions (C; posterior parietal cortex, PPC; medial prefrontal cortex, mPFC; lateral temporal cortex, LTC; and medial parietal cortex, mPC, right panel) showed a speed-dependent modulation by running direction with six-fold rotational symmetry. Right panel in B shows average fMRI signal over the entire time series of all voxels in the entorhinal cortex for all directions of aligned (red) and misaligned (gray) fast runs. Adapted from Doeller and others (2010).

Clinical Implications: From Systems to Symptoms

Getting lost is one of the most common initial presentations in Alzheimer's disease. A degraded place cell representation of the spatial environment is found both in transgenic mouse models of Alzheimer's disease (Cacucci and others 2008) and in old rats (Barnes and others 1997). This deficit in representing space might explain the general decline in memory performance in patients with neurodegenerative diseases and during old age. For instance, patients with selective damage to the hippocampus (Hartley and others 2007) as well as patients with Alzheimer's disease (Bird, Chan, and others 2010) show

a specific impairment in processing the environmental geometry rather than other aspects of visual scenes (see also Lee and others 2005; Hort and others 2007; Pengas and others 2010). Thus, behavioral tests of spatial memory might be a useful diagnostic tool for the early detection of Alzheimer's disease and an indicator for hippocampal damage. An interesting direction for future research would be to measure the grid-cell like fMRI signal in entorhinal cortex and the relationship to memory in patients with neurodegenerative disease (and the elderly). This approach might lead to the development of functional MRI markers of Alzheimer's disease that could potentially extend recent developments of structural MRI biomarkers (Kloppel and others 2008).

Conclusion

By translating findings from the single cell level in rodents, we identified proxy measures of place and grid cell–like activity at the systems level in the human brain and showed how these specific neural representations support spatial behavior and memory formation. The combination of single-unit electrophysiology with neuroimaging in systems neuroscience ("electrophysiologically informed neuroimaging") could potentially produce a coherent understanding of brain function from neural representations to systems-level involvement in behavior. This approach might also allow us to better understand the neural mechanisms underlying memory impairments in neurodegenerative diseases.

Declaration of Conflicting Interests

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