Spatial Cognition and the Hippocampus: The Anterior–Posterior Axis

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Abstract

■ We discuss the question of differentiation along the anterior–posterior longitudinal axis of the hippocampus. Data from a recent fMRI study are reanalyzed to determine whether activations in these hippocampal regions are affected by the nature of the information being accessed during a scanning session in which participants thought about episodes from their lives. Retrieving detailed spatial relational information preferentially activated the posterior hippocampus, whereas retrieving information about locales (or contexts) preferentially activated the anterior hippocampus. These data support the view that there is functional differentiation along the longitudinal axis in humans that matches what has been seen in rats, namely, that the posterior (dorsal) hippocampus is crucial for precise spatial behavior, and the anterior (ventral) hippocampus is crucial for context coding. ■

INTRODUCTION

In the 1960s, a conundrum faced those of us interested in the hippocampus: The effects of damage to that structure seemed to differ between humans and rats. As the study of H.M. showed (Scoville & Milner, 1957), the major impact of such damage was a severe amnestic syndrome. Suzanne Corkin's dissertation work was instrumental in sharpening our understanding of the nature of the memory loss, providing some of the first evidence that there were limits to this loss (Corkin, 1968). However, Orbach, Milner, and Rasmussen (1960) had shown that experimental lesions in the monkey thought to parallel the damage caused by H.M.'s surgery failed to elicit significant memory loss. As a consequence, researchers focusing on hippocampus in primates and rodents talked about hippocampal function not in terms of memory but rather of such things as response inhibition (e.g., Kimble, 1963; Isaacson & Wickelgren, 1962).

One of us (L.N.) began his graduate studies at McGill just as Corkin was finishing hers and, given an interest in the hippocampus in rats, had to face this conundrum head-on. One possible story was that the hippocampus played different roles in humans and other species. Although there is an element of truth to this notion, in that the human hippocampus plays a role in verbal memory that it cannot play in other primates and rodents, this hypothesis was not very satisfying if one believed in evolutionary continuity. It was hard to accept the idea that this brain region, whose structure seemed to be highly conserved across vertebrates, suddenly came to play a memory role in humans that it did not play in any other species.

One possibility presented itself at the time: Perhaps, the parts of the hippocampus that were under investigation in humans and other animals were not the same. This was not such a crazy idea: One impact of the evolutionary explosion of neocortex was to literally shift the location of the hippocampus in the brain. The anatomical location of the hippocampus is quite different in the rat and the human. H.M.'s surgery primarily affected the anterior portions of his hippocampus (and medial-temporal lobe; Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997), which are the equivalent of the ventral hippocampus in the rat. As it happens, the ventral hippocampus in the rat is quite a bit harder to reach (with electrodes or cannulae) than the dorsal hippocampus, so most of the studies done in rodents at this time were aimed at the dorsal part of this structure. Thus, the possibility emerged that there might be important functional differences between the dorsal and ventral hippocampus in rats and, similarly, between the posterior and anterior hippocampus in humans and that such functional differences could solve the conundrum.

This possibility motivated L.N.'s doctoral research, which compared the effects of dorsal and ventral hippocampal lesions in rats on a number of behavioral tasks, including exploration, avoidance learning, and fear conditioning. Although some differences were observed between the groups (Nadel, 1968) and functional differences between dorsal and ventral hippocampus had been reported by two others (Grant & Jarrard, 1968; Hughes, 1965), none of these differences fell neatly into a memory versus response inhibition framework. In short, the conundrum remained.

Matters changed with the development of the notion of multiple memory systems, first proposed by researchers studying the hippocampus of animals (cf. Gaffan, 1974;

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Hirsh, 1974; Nadel & O'Keefe, 1974). Coupled with the discovery of "place cells" that linked the hippocampus in rats to spatial cognition (O'Keefe & Nadel, 1978; Nadel & O'Keefe, 1974; O'Keefe & Dostrovsky, 1971), the outlines of a resolution emerged. The hippocampus in all species is engaged in memory but only of a certain sort: spatial memory in rats and episodic memory in humans, perhaps because the latter necessarily involves spatial contextual information (O'Keefe & Nadel, 1978). As this consensus resolution emerged, the question of differentiation of function along the longitudinal axis of the hippocampus faded into the background.

Some years later, Jung, Wiener, and McNaughton (1994) showed that there was an important difference between the dorsal and ventral hippocampus with regard to the properties of the place cells in these two regions. Place cells are distinguished by the fact that they respond quite selectively in any given environment, in a region of that environment known as the "place field." What Jung et al. showed was that the size of place fields changed systematically as one moved along the longitudinal axis of the hippocampus. Place cells in the dorsal end have relatively small fields, which get progressively larger as one proceeds toward the ventral end of the hippocampus. Kjelstrup et al. (2008) recently extended these findings by testing rats on an 18-m linear track. In this environment, they observed place cells in the far reaches of the ventral hippocampus that had fields 10 meters in diameter. We know now that this spatial grain gradient is replicated in another key element of the spatial mapping system, namely the so-called grid cells in the medial entorhinal cortex (MEC; Moser, Kropff, & Moser, 2008). Exactly how to understand these gradients (if indeed they are gradients rather than discrete modules; cf. Stensola et al., 2010) remains unclear. At the same time, lesion studies began to demonstrate consistent differences between dorsal and ventral hippocampus—frequently, the emphasis has been on the spatial navigational functions of the dorsal hippocampus and some poorly specified role of the ventral hippocampus in anxiety and context fear learning (Hunsaker, Fieldsted, Rosenberg, & Kesner, 2008; Rogers, Hunsaker, & Kesner, 2006; Rudy & Matus-Amat, 2005; Maren & Holt, 2004; Pothuizen, Zhang, Jongen-Relo, Feldon, & Yee, 2004; Bannerman et al., 1999). It is important to note that dorsal and ventral hippocampus appear to have quite distinct patterns of inputs and outputs (Libby, Ekstrom, Ragland, & Ranganath, 2012; Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008); for example, direct connections between amygdala and ventral, but not dorsal, hippocampus have often been taken as evidence for a ventral role in fear (see Fanselow & Dong, 2010, for a recent review).

Reports of differential activation patterns in posterior and anterior hippocampus began to appear in fMRI studies in human hippocampus. One common finding is that activity in the anterior hippocampus reflects reactions to novelty, whereas activity in posterior hippocampus is more closely tied to spatial cognition (Duncan, Ketz, Inati, & Davachi, 2012; Strange, Fletcher, Henson, Friston, & Dolan, 1999; Stern et al., 1996). Coming at this issue from another perspective, Poppenk and Moscovitch (2011) used structural and functional connectivity data to make the point that the posterior, but not the anterior, hippocampus is closely related to episodic memory retrieval. This is consistent with findings reported by Greicius et al. (2003), who showed that posterior, but not anterior, hippocampal activation was associated with episodic memory encoding and retrieval. A recent study in our laboratory took yet another approach to this question. Hoscheidt, Nadel, Payne, and Ryan (2010) investigated the role of the hippocampus in retrieval of spatial context within and across episodic and semantic memory domains. To do this, participants were initially given a questionnaire that covered various events in their lives: some relatively recent, others more remote. On the basis of this questionnaire, we created a set of questions tailored to each participant for use in the scanner. These questions were created so as to probe both episodic and semantic memory of either a spatial or nonspatial nature.

Readers are referred to the original article for a detailed description of the results. Basically, the study showed that retrieval of episodic memory and spatial information elicited functional activation at different locations along the anterior–posterior axis of the hippocampus. The episodic memory condition drove robust activation in the anterior hippocampus, whereas the posterior hippocampus showed more selective activation for the retrieval of spatial information, whether the source of this spatial information was from a past experienced event or well-established world knowledge.

A similar pattern was observed in another recent study from our laboratory (Ryan, Lin, Ketcham, & Nadel, 2010) in which participants were shown arrays of objects and were later asked to make relational judgments regarding pairs of objects. The judgments focused either on the spatial relations between the objects or a comparison of other nonspatial attributes, such as which of the two objects was more expensive. Regardless of whether the spatial information was based on attributes of the array itself (episodic) or real-world attributes of the objects (semantic), spatial relational judgments resulted in activation that extended into posterior hippocampus particularly in the right hemisphere, whereas activations during nonspatial judgments were confined to anterior hippocampus.

Taken together, these findings are consistent with the notion that the posterior hippocampus plays an integral role in spatial cognition regardless of the type of memory (episodic or semantic) being retrieved. Differences in location of activation along the anterior–posterior axis of the hippocampus may be driven, at least in part, by two things: (1) the type of information being processed within the medial-temporal lobe and (2) differences in input from supporting brain structures into anterior and

posterior hippocampal regions during memory and spatial retrieval.

Our interest in further deciphering the functional differentiation along the longitudinal axis led us to perform a few subsidiary analyses of the data from Hoscheidt et al. (2010), and it is the results of these analyses, which aimed to compare posterior and anterior hippocampal activations during retrieval of different types of spatial information, that we report in this note. These findings, although limited in scope, support an approach to the posterior–anterior (or dorsal–ventral) gradient that might help us understand both human and rat data and, in so doing, address the species conundrum. But, we are getting a bit ahead of ourselves. It would be best to briefly describe the results in question.

METHODS

Participants

Seventeen healthy undergraduates (nine women, mean age = 22.2 years, range = 18–30 years) were recruited from the University of Arizona participant pool. Participants were screened for neurological and psychiatric disorders, past and present drug or alcohol abuse, history of head injury with sequelae, and contraindications to MRI. The University of Arizona Human Subjects Committee approved all procedures used in the current design. Volunteers gave informed consent before behavioral and neuroimaging sessions and were given course credit in exchange for participation.

Materials

For this article, materials and methods described focus on one (i.e., episodic) of the two memory conditions that were part of the larger study (see Hoscheidt et al., 2010, for full experimental design). Episodic materials used for the imaging session were collected during a 2-hr autobiographical interview conducted in the laboratory 1 week before scanning. Participants were presented with a list of 100 common life events (taken from Ryan et al., 2001) and were instructed to choose 30 events for which they had a unique memory from their personal past, for example, "a job interview" or "attending a wedding." Participants were instructed to choose only life events from the list for which they had a specific memory that they could recollect in detail, including the specific time and place the event occurred. Participants chose five events from the list at one time and were asked a series of semi-standardized questions about each event. Questions were designed to elicit recollection of various spatial aspects of each event, specifically the location in which the event transpired (e.g., "Where was your sister's wedding held?") and spatial relationships among objects and/or people (including the rememberer) involved (e.g., "Who sat to your right during the wedding?"). Participants were asked to report when in their life the event occurred and whether the event was positive, negative, or neutral. All participants were young adults (mean age = 22 years); thus, memories reported during interviews were relatively recent, occurring within the past 5 years, and included both positive and negative events.

Information from the autobiographical interview was used to create true participant-specific episodic statements that were presented 1 week later in a true/false recognition paradigm in the scanner. These statements were designed to cue participants to recollect spatial relationships between people (including the rememberer) or objects present during a particular event, for example, "During your sister's wedding, your mother sat to your right" or the specific location in which an event transpired, for example, "Your prom was held at the Hilton Hotel" (see Table 1). Each spatial condition contained an equal number of statements created from positive, negative, and neutral memories to control for potential effects of emotion. Sentence length was matched across spatial conditions, and critical information required to make a true/false judgment was contained in the last word of each sentence. The control condition contained ungrammatical sentences composed of prepositions and conjunctions, designed to account for functional activation associated with reading and motor responses, for example, "Unless like off without while if once nor" (Maguire & Mummery, 1999).

Neuroimaging Procedure

One week after the initial autobiographical interview, participants came to the university medical center to undergo functional neuroimaging. To ensure that participants understood the task before functional data collection, they received detailed instructions and were required to perform a short practice on a computer outside the scanner. Before the practice session, participants were provided with the experimental task instructions. Participants were instructed to judge whether statements presented over the computer screen were true or false and to indicate their

Table 1. Two Spatial Conditions Used for "True or False" Recognition Task in the Scanner

Location	The location of a past experienced event. e.g., "Your parents' 25th wedding anniversary party was held at the Marriott Resort."
Spatial relations	The spatial relationship between the rememberer and/or a person or object present during a past experienced event. e.g., "When your mom spilled her wine at dinner, your dad was sitting to your left."

decision by making a mouse button press. To avoid inadvertently cuing participants for past personal events that they would be tested on during experimental trials, all statements presented during the practice session were hypothetical statements created by experimenters. Participants were informed that this would be the case during the practice session only and were instructed to randomly choose statements to respond to as true and false so that they could practice responding with the appropriate button press. For control sentences, participants were instructed to read the ungrammatical sentence carefully and to make a right mouse button press when finished. Upon completion of the practice session, participants were oriented to fMRI procedures; were fitted with earplugs, headphones, and high-resolution goggles; were placed supine on the MRI table; and had their head stabilized with cushions.

During functional scanning, experimental stimuli were presented to participants through high-resolution goggles (Resonance Techonologies, Inc., Northridge, CA) using the stimulus presentation program DMDX (Version 3.1.4.1; Forster & Forster, 2003). To ensure accurate synchronization of stimulus onset and volume acquisition for event-related data analysis, DMDX was programed to trigger the start of each functional scan and record stimulus onset times, button press responses, and RTs. True/false spatial episodic statements were presented across two functional scans in a pseudorandomized fashion. In total, participants were presented with 34 episodic statements: 30 true (15 relations, 15 location), 4 false (2 relations, 2 location), and 30 control sentences. All statements and control sentences were preceded by a 3-sec ("True or False" or "Read") cue to alert participants to the trial type that followed. True/false statements and control sentences were presented for 8 sec regardless of the participant's response time, and trials were separated by a 1-sec ISI. Behavioral performance on the true/false recognition task was near 100% for all participants.

Image Acquisition and Analyses

Images were collected using a four-channel phased array head coil on a 3.0-T Signa VH/i whole body scanner (Signa Echo Speed; General Electric, Milwaukee, WI). A sagittal localizer was collected in three planes of section for image alignment, followed by a high-resolution 3-D spoiled gradient recall anatomical scan (1.5-mm sagittal sections covering whole brain, matrix = 256 × 256, flip angle = 30, repetition time = 22 msec, echo time = 3.0 msec, field of view = 25 cm). A total of four functional scans (375 volumes × 2 scans; 293 volumes × 2 scans), aligned axially parallel to the AC–PC plane, were acquired using a single-shot spiral in–out pulse sequence (Glover & Law, 2001; matrix = 64, repetition time = 2,040, echo time = 30, sections = 30, and field of view = 240 × 240 mm, 4 mm, no skip). Each scan lasted approximately 12 min, for a total scan time of approximately 45 min.

fMRI data were analyzed using SPM5 software (Wellcome Department of Cognitive Neurology, London, United Kingdom; www.fil.ion.ucl.ac.uk/spm/software/spm5). Images were reconstructed off-line and underwent motion correction, spatial normalization, slice timing correction, and smoothing, as described in detail in Hoscheidt et al. (2010). First-level analyses (single-subject) were conducted using the general linear model implemented in SPM5. Experimental and control conditions were modeled using an event-related design (duration equal to zero) and convolved with the canonical hemodynamic response (HDR) function. Estimation of the onset time of the HDR was modeled to stimulus onset for each condition. Contrast images comparing HDR estimates for true spatial and control conditions that yielded correct responses were calculated using SPMs. Contrast images for each participant were submitted to a random-effects group analysis using a one-sample t test (Friston, Holmes, Price, Buchel, & Worsley, 1999). A false discovery rate (FDR) correction for multiple comparisons was applied to the simple contrasts for the group analysis (Genovese, Lazar, & Nichols, 2002). Activations in the hippocampus were considered significant at $p < .05$, FDR corrected. An ROI analysis was conducted on the right and left hippocampus using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002) to (1) determine whether spatial conditions (minus the control task) elicited activation in distinct or shared regions and (2) to examine where along the anterior–posterior axis of the hippocampus activations for each spatial condition resided. Functional ROIs were defined as more anterior or posterior based on their center of mass on the y axis, relative to one another, and were categorized as one of the following: (1) anterior, (2) anterior middle, (3) posterior middle, or (4) posterior. Anterior–posterior labeling of ROIs in the left hippocampus remained consistent with the categorization schema on the right, such that a y-axis center of mass defined as posterior in the right hippocampus would also be considered posterior in the left hippocampus. Effect sizes were extracted from functional ROIs from the direct contrast of spatial conditions. This was done to examine activation patterns along the anterior–posterior extent of the hippocampus for each spatial condition within a direct contrast.

RESULTS AND DISCUSSION

Brain images provided in Figure 1B and 1D show ROI results for random effects analyses comparing spatial conditions to the control task, within the right and left hippocampus. ROIs are color-coded to illustrate regions of activation that were selective for a particular spatial condition (location: green, relations: red) and a region of activation that was common across both spatial conditions. The region of common activation, a large area in the middle hippocampus, was divided into two equal parts and defined as anterior-middle (violet) and posterior-middle (blue) regions to better examine anterior–posterior gradients

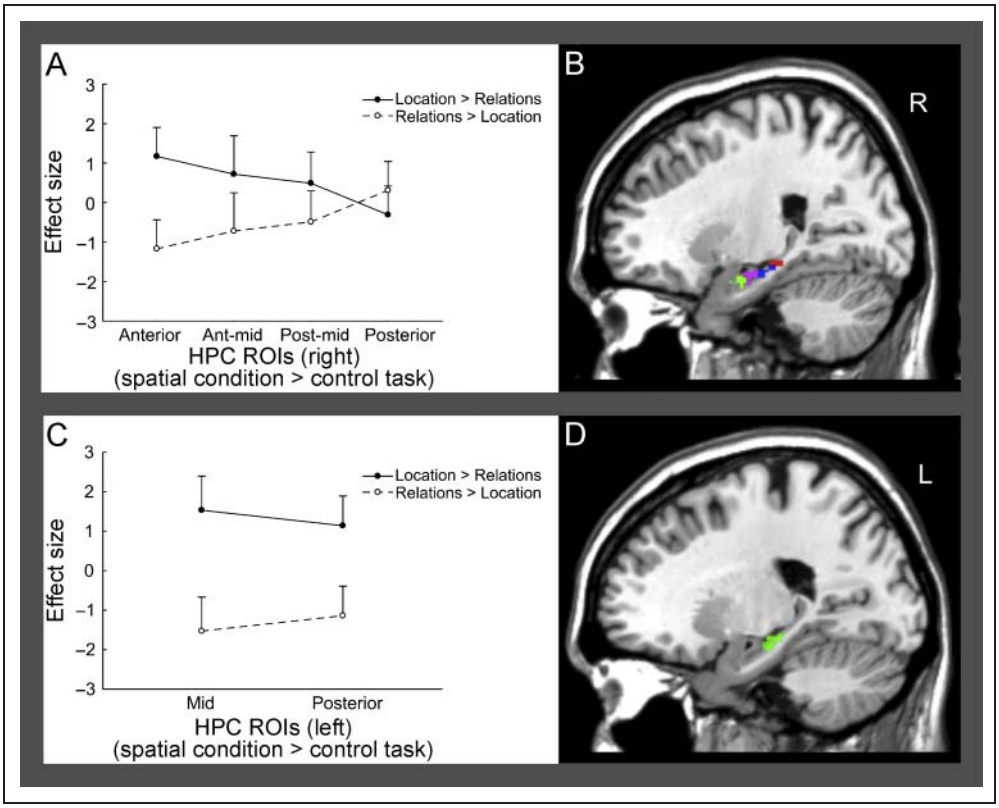

Figure 1. Brain images show MarsBAR ROI analysis, within the right (B) and left (D) hippocampus, for SPM5 contrasts of each spatial condition minus the control task ($p < .05$, FDR corrected, whole brain). Spatial condition-specific activation and a shared region of overlap are shown along the anterior–posterior extent of the right and left hippocampus in different colors (location-specific = green, relations-specific = red, overlapping = violet and blue). Graphs show effect sizes extracted from ROIs for contrasts of spatial conditions compared directly, within the right (A) and left (C) hippocampus.

along the longitudinal axis of the hippocampus with respect to the effect-size analyses.

As illustrated in Figure 1B, the two spatial conditions preferentially activated different zones along the anterior–posterior axis of the right hippocampus. The anterior portion of the hippocampus showed greater activation for retrieval of answers concerning locations (green), whereas greater activation in more posterior regions occurred during retrieval of answers concerning spatial relations (red). Both spatial conditions elicited activation in the middle portion of the hippocampus (violet and blue) between the anterior and posterior regions of activation noted above that were location- and relation-specific.

The left hippocampus showed a pattern of activation that was similar to the right in some, but not all, respects (see Figure 1D). Similar to the right hippocampus, the spatial relations condition elicited activation primarily in a more posterior region of the hippocampus; however, unlike the right hippocampus, this region was also activated by the location condition (note: this ROI was more medial to the sagittal plane of view provided and is not shown). The location condition additionally elicited activation in a more middle–posterior portion of the hippocampus, a region that showed selective activation for retrieval of location.

To examine functional activation elicited by each spatial condition along the anterior–posterior extent of the hippocampus, while accounting for activation elicited by the opposing spatial condition, effect sizes were extracted from ROIs using contrasts that directly compared activation for spatial relations and location (Figure 1A and C). This analysis was performed to test the prediction that activation in the right hippocampus for locations (minus relations) would show greater activation in the anterior, compared with posterior, hippocampus with a gradual decrease in activation across the middle regions. By contrast, effect sizes extracted for relations (minus locations) would show the inverse pattern, a gradual increase in activation from anterior to posterior regions. As direct contrasts necessarily result in effect sizes from one contrast being the inverse of the other, inclusion of interaction effects between spatial conditions would be inappropriate and is not discussed. Instead, we focus on paired t test comparisons of effect sizes along the anterior–posterior extent of the hippocampus within each contrast. Paired t test results from the right hippocampus supported our hypothesis, showing that anterior and posterior effect sizes were significantly different ($t = \pm 3.12$, $p = .006$) within each spatial contrast (Figure 1A). Functional activation elicited by the location (minus relations) condition was significantly greater in the anterior compared with the posterior hippocampus. The reverse pattern was then true for functional activation elicited by the spatial relations (minus location) condition, significantly greater activation in the posterior compared with the anterior hippocampus. By comparison, effect sizes extracted from ROIs in the left hippocampus were not significantly different (Figure 1C), although only two ROIs were observed,

both located in more middle-to-posterior regions of the hippocampus.

To summarize, the main result of these analyses concerns the patterns of activation triggered by answering two rather different kinds of spatial question. One kind of question required that the participant think about the spatial relations between at least two things—this could include relations of direction (left–right, up–down, and front–back) or distance (near–far). The second kind of question required that the participant think about a place, or context, as a unit (one's house, the city where an event occurred, etc.). Such locales are typically easy to name and indeed may be generally accessed through language.

We observed a distinction between posterior and anterior hippocampus in response to these two kinds of questions. Questions about spatial relations preferentially engaged the posterior hippocampus, whereas questions about spatial locales or contexts preferentially engaged the anterior hippocampus. It is worth noting that this distinction was most robustly observed in the right hippocampus, also consistent with our previous work using object arrays (Ryan et al., 2010). In the left hippocampus, there was activation of the more middle–posterior region by location-type questions, but no specific activation of the posterior hippocampus by relational questions. This difference might reflect the use of verbal labels and that labeling a place is trivially easy and virtually automatic, whereas labeling relations in a scene is possible but less likely.

What does this posterior–anterior differentiation tell us about the conundrum we discussed at the outset? And how does it mesh with what we know about the dorsal–ventral gradient in rats? To address these questions, we need to look more closely at the grid cell network in MEC, which, as we noted already, shows a similar spatial grain gradient along the dorsal–ventral axis. MEC grid cells at the more dorsal end have grids with smaller internode distances than do those at the ventral end. In principle, this gradient could be organized in a continuous way such that, as one moves along the longitudinal axis, there is a steady increase in the grain or there could be discontinuities of some form. Recent work from the Moser's group (e.g., Stensola et al., 2010) supports the latter possibility. They recorded from MEC grid cells while the rat was moving about a familiar environment. This established the internode distances for their grid cells before the crucial manipulation, which involved compressing the physical environment and then determining the response of the grid cells to this change in space. They found what appears to be a set of discontinuities along the longitudinal axis. At the most dorsal end, the network of grid cells responded to environmental compression with minimal rescaling, thereby preserving the geometric information encoded in the network. At the most ventral end, a rather different effect was observed. Here, compression of the environment led to significant rescaling, which resulted in the entire representation surviving, although with altered geometry (distances). To put this difference simply: At the dorsal end, spatial details are preserved, whereas at the ventral end, the sense of the particular place is maintained at the expense of losing geometric validity. It is not a large leap from these data to the notion that the dorsal end, given its access to precise spatial detail, would be most useful in navigational tasks, whereas the ventral end would be most useful in identifying the place or location one was in.

This is what we believe we have observed in our imaging data. Questions about spatial relations require that the participant think about specific details that are best represented in the posterior (dorsal) hippocampus. Questions about spatial location require that the participant think about contextual information best represented in the anterior (ventral) hippocampus.

Is this a resolution to the conundrum? Perhaps. Clearly, different regions within the hippocampus seem to play somewhat different roles. This happens although the individual elements in these regions appear quite similar; for example, there are place cells all along the longitudinal axis of the hippocampus and grid cells along the axis of the entorhinal cortex. We discussed above the recent work with rats suggesting that important differences emerge at the network level: Cells at different ends of the MEC (and we presume, hippocampus) behave quite differently in response to an environmental challenge. At the dorsal end, spatial detail is preserved; at the ventral end, place is preserved. As a consequence, the representations formed in dorsal hippocampus are the sort that would be critical for navigation, whereas the representations formed in ventral hippocampal representations are critical for context. The present results, in humans, suggest that the posterior hippocampus is preferentially engaged by thinking about spatial details (of the sort one might use in navigating), whereas the anterior hippocampus is preferentially engaged by thinking about locations or contexts. At this level of description, one could say that the hippocampus in rats and the hippocampus in humans are doing essentially the same thing.

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