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Review

Imaging the Human Medial Temporal Lobe with High-Resolution fMRI

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High-resolution functional MRI (hr-fMRI) affords unique leverage on the functional properties of human medial temporal lobe (MTL) substructures. We review initial hr-fMRI efforts to delineate (1) encoding and retrieval processes within the hippocampal circuit, (2) hippocampal subfield contributions to pattern separation and pattern completion, and (3) the representational capabilities of distinct MTL subregions. Extant data reveal functional heterogeneity within human MTL and highlight the promise of hr-fMRI for bridging human, animal, and computational approaches to understanding MTL function.

Introduction

Since Scoville and Milner's (Scoville and Milner, 1957) landmark study of functional deficits in patients with medial temporal lobe (MTL) lesions, extensive evidence has established the critical role of this region in declarative memory—i.e., memory for facts and events (Eichenbaum and Cohen, 2001; Squire, 1992). However, the manner in which specific substructures within the MTL contribute to declarative memory remains a topic of debate. Computational neurobiological models and emerging rodent data suggest that differences in intrasubfield anatomy and connectivity underlie MTL subregional differences in mnemonic function (e.g., Lee et al., 2004; Leutgeb et al., 2007; Leutgeb et al., 2004; O'Reilly and McClelland, 1994; Rolls and Kesner, 2006; Treves and Rolls, 1994; Vazdarjanova and Guzowski, 2004). In humans, however, the vast majority of MTL lesion and functional neuroimaging studies lack the spatial resolution to examine subfield contributions to declarative memory, making crucial comparisons with the computational and animal literatures difficult. Accordingly, increased anatomical precision is required to test extant models of MTL function and to advance understanding of the functional heterogeneity that is undoubtedly present within the human MTL.

Over the past decade, investigators have begun to implement high spatial resolution functional magnetic resonance imaging (hr-fMRI) of human MTL in which anatomical landmarks correlating with MTL cytoarchitectonics are used to guide segmentation of the MTL into component hippocampal subfields and surrounding cortical structures. Guided by MTL atlases (Duvernoy, 2005; Insausti and Amaral, 2004) and standards developed in structural MRI studies of the MTL (Insausti et al., 1998; Pruessner et al., 2002; Pruessner et al., 2000), investigators can now routinely segment human hippocampus into the subiculum, CA_1, and a combined subregion consisting of the dentate gyrus, CA_2, and CA_3 ($DG/CA_{2/3}$; these subfields are difficult to unambiguously segment at current functional MR resolutions). Moreover, the anterior extent of the parahippocampal gyrus can be divided into entorhinal cortex (ERC) and perirhinal cortex (PRC) and differentiated from parahippocampal cortex (PHC) in the posterior portion of the gyrus (Figure 1A).

Here, we briefly review the development of hr-fMRI approaches to studying human MTL function and highlight three core issues that have been explored in the hr-fMRI literature to date: (1) encoding and retrieval distinctions between input and output components of the hippocampal circuit; (2) differential involvement of hippocampal subfields in pattern separation and pattern completion; and (3) the nature of hippocampal and MTL cortical representations as addressed by multivariate pattern analysis. We conclude by considering remaining challenges for high-resolution functional imaging of the MTL, as well as future directions that promise to further advance understanding of how the MTL mediates memory.

High-Resolution fMRI of the MTL

Within the neuroimaging literature, the term "high-resolution fMRI" is generally used to refer to functional imaging of a specific portion of the brain at higher spatial resolution than is typically acquired (e.g., ≤ 1 mm^3 in visual cortex; Grill-Spector et al., 2006). In studies of human MTL, the in-plane resolution of hr-fMRI voxels is typically $\leq 2 \times 2$ mm^2, as compared with standard-resolution fMRI data that are often acquired at in-plane resolutions of $\geq 3 \times 3$ mm^2. This enhanced spatial resolution, along with resolution-preserving data analysis procedures (see below), allows for localization of blood oxygen level-dependent (BOLD) activity to individual MTL subfields, with activation in a given voxel being an indirect hemodynamic proxy for signals from many thousands of underlying neurons (Logothetis, 2008). This high-resolution approach is well suited to address questions pertaining to the relative contributions of MTL subfields to specific aspects of mnemonic processing.

The use of hr-fMRI to explore human MTL subfield function was first described by two research teams almost a decade ago. Small et al. (2000a and 2000b) examined resting-state activity using conventional T2*-weighted gradient-echo images at 1.5T (5 slices, 0.9 × 0.9 × 5 mm resolution), and Zeineh et al. (2000) examined MTL novelty encoding effects using a T2*-weighted gradient-echo echo-planar imaging (EPI) sequence at 3T (16 slices, 1.6 × 1.6 × 3 mm resolution). In both

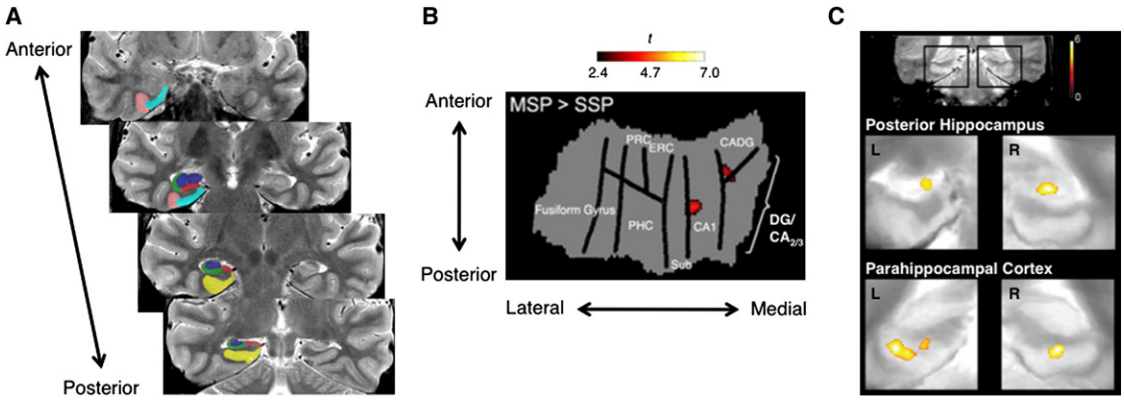

Figure 1. Subfield Analysis Methods

(A) High-resolution anatomical images of human MTL displaying manually drawn hippocampal ROIs: CA_1 (green), $DG/CA_{2/3}$ (blue), and the subiculum (red), as well as PRC (pink), ERC (cyan), and PHC (yellow).

(B) Group subfield activity projected onto a flattened representation of the MTL demonstrating greater CA_1 involvement in navigating a virtual town from multiple (MSP) relative to single starting points (SSP). This figure is modified from a figure in Suthana et al. (2009a), with permission from the Society for Neuroscience.

(C) Group-level statistical maps overlaid on a representative participant's anatomical images demonstrating performance-related probe period activity on a delayed-match-to-sample task in posterior hippocampal and parahippocampal regions. This figure is modified from a figure in Olsen et al. (2009), with permission from the Society for Neuroscience.

cases, acquisition was perpendicular to the long axis of the hippocampus, yielding high resolution in the coronal plane of the hippocampus and surrounding cortex and, thus, affording increased substructure visualization. During data analysis, participant-specific anatomically defined regions of interest (ROIs) were demarcated, using either the high-resolution functional images themselves (Small et al., 2000a, 2000b) or a separate set of coregistered structural images with even higher spatial resolution (0.4 × 0.4 × 3 mm; Zeineh et al., 2000). Average signal intensity was extracted from each subfield from each participant and then submitted to group-level (across-participant) statistical analysis. Moreover, to better visualize subfield boundaries and the topography of functional activation in the MTL, Zeineh and colleagues developed a method for flattening the gray matter MTL ribbon into a two-dimensional representation (see Figure 1B for a recent demonstration of the flat map technique), adapted from flat map methods routinely used to study the visual cortex (e.g., Van Essen et al., 1998).

Since these initial reports, most subsequent hr-fMRI studies of human MTL have been conducted at 3T and have collected both high-resolution functional and structural volumes, with the latter having superior resolution that allows for demarcation of anatomical ROIs. To ensure that these higher-resolution ROIs are properly aligned with the corresponding regions in the functional data, researchers typically use one of several standardized within-participant linear coregistration tools. Moreover, to preserve the high resolution of the functional images, most hr-fMRI studies forgo the practice of spatial smoothing or else apply only minimal smoothing within the boundaries of each MTL substructure in an effort to boost the signal-to-noise ratio (SNR) for voxel-level analyses.

With respect to cross-participant coregistration, voxel-level group analyses of fMRI data from the MTL are inherently challenging because the small sizes of MTL subregions render them particularly vulnerable to misregistration across individuals. For this reason, hr-fMRI studies often refrain from conducting voxel-level group analyses, instead favoring the anatomically defined ROI analysis approach described above (Figures 1A, 2B, and 3B). Though this method eliminates the need for cross-participant registration, it yields data averaged across the entirety of a given ROI. Thus, it does not enable potentially informative observations of the topographic distribution of activation within a subfield and can suffer from reduced sensitivity due to the averaging of signal from functionally responsive and nonresponsive voxels. Fortunately, recent advances in cross-participant registration techniques, such as fully deformable nonlinear registration algorithms (Ekstrom et al., 2009b; Yassa and Stark, 2009), allow for reliable voxel-level evaluation of high-resolution MTL activity at the group level (Figures 1B, 1C, and 3A). Such techniques afford group-level analyses by warping each participant's MTL subfields to match the corresponding subfields on a template image. In this way, activation patterns consistent across participants can be readily visualized, allowing for localization of subfield activity along the full anterior-posterior extent of the MTL. Finally, recent hr-fMRI studies have benefited from continued advances in MR hardware (e.g., improved gradients, parallel imaging), pulse sequence development (e.g., spiral in/out), and data analysis techniques (e.g., multi-voxel pattern analysis).

Encoding and Retrieval within Human Hippocampus

Numerous standard-resolution fMRI studies have documented MTL activity during episodic encoding and retrieval (e.g., Brewer et al., 1998; Eldridge et al., 2000; Wagner et al., 1998; Yonelinas et al., 2005; for reviews, see Davachi, 2006; Diana et al., 2007; Schacter and Wagner, 1999), leading to increased specificity regarding the differential roles of the hippocampus and surrounding MTL cortices in declarative memory. While informing theories of hippocampal versus cortical contributions to memory (e.g., Brown and Aggleton, 2001; Eichenbaum et al.,

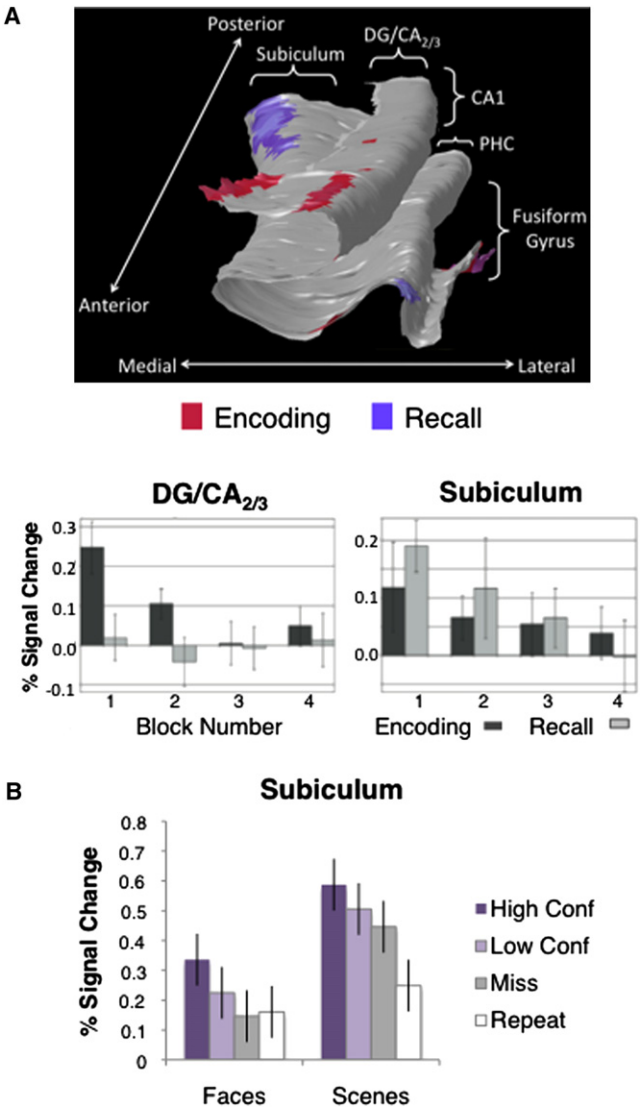

Figure 2. Hippocampal Encoding and Retrieval Effects

(A) Subfield activity projected onto a flattened representation of the MTL demonstrating encoding activity in DG/$CA_{2/3}$ and retrieval activity in the subiculum. Flatmap is accompanied by bar graphs indicating averaged activity in DG/$CA_{2/3}$ and the subiculum across four consecutive blocks in which participants encoded and recalled the same face-name associations. This figure is modified from a figure in Zeineh et al. (2003), with permission from AAAS.

(B) Averaged subicular activity in response to faces and scenes presented once or repeatedly. Stimuli presented once were subsequently tested outside the scanner, with memory performance used to back-sort encoding trials as recognized with high confidence, low confidence, or missed. This figure is modified from a figure in Preston et al. (2010), with permission from MIT Press.

2007; McClelland et al., 1995; Norman and O'Reilly, 2003), the limited spatial resolution of most fMRI studies has generally prevented progress toward understanding the role of specific hippocampal subfields in learning and remembering.

Two of the earliest hr-fMRI studies of the MTL directly examined hippocampal encoding and retrieval and yielded striking findings suggesting that a functional distinction may exist between input and output structures of the trisynaptic hippocampal circuit, with input structures (DG/$CA_{2/3}$) being selectively active during successful encoding and output structures (CA_1 and subiculum) being differentially active during successful subsequent retrieval (Eldridge et al., 2005; Zeineh et al., 2003). In the first of these studies, Zeineh et al. (2003) scanned participants as they performed a face-name association task across a series of alternating encoding and recall blocks. During associative encoding, activity levels in DG/$CA_{2/3}$, but not in subiculum, closely tracked participants' learning curve, whereas during face-cued recall for the associated name, activity in subiculum, but not in DG/$CA_{2/3}$, tracked performance (Figure 2A). In the second of these studies, Eldridge et al. (2005) used an event-related paradigm to link activation changes to memory success on an item-by-item basis. In this study, participants initially were scanned as they intentionally encoded a series of object pairs and again the next day as their memories were tested. Through a subsequent memory analysis (for reviews, see Blumenfeld and Ranganath, 2007; Paller and Wagner, 2002; Spaniol et al., 2009; Uncapher and Wagner, 2009), retrieval performance was used to back-sort encoding trials according to whether each item was associated with vivid recollection, familiarity, or forgetting. The activation profile of DG/$CA_{2/3}$ suggested selective involvement in the formation of new memories: encoding activity was correlated with subsequent memory success, and retrieval activity was greater for correctly rejected foils (i.e., novel items) than for successfully recognized pairs. By contrast, CA_1 encoding activity was not clearly related to subsequent memory performance, whereas retrieval-related activation was greater for recollected than forgotten items. In subiculum, encoding activity demonstrated a complex relationship to later memory outcome, being greater for later familiar than later forgotten or recollected items; at retrieval, subicular activity clearly tracked recollection success, being greater for recollected than for familiar or forgotten items.

Three recent hr-fMRI studies have revealed related intra-hippocampal functional dissociations during episodic encoding and retrieval. In an experiment examining the degree to which MTL subfields are recruited during the study, delay, and probe phases of a delayed-match-to-sample (DMS) face memory task, Olsen et al. (2009) observed a subregion × task phase interaction, wherein DG/$CA_{2/3}$ was differentially active during the study and delay phases of the task, during which encoding operations predominate, whereas CA_1 and subiculum were differentially active during the probe (retrieval) phase. Furthermore, in a pair of experiments examining the encoding (Carr et al., 2009) and retrieval (Viskontas et al., 2009) of durable episodic memories—that is, memories retaining their episodic quality over a one-week delay—a significant subsequent memory effect was selectively observed in DG/$CA_{2/3}$ at encoding, whereas during retrieval, recollection was selectively associated with activation in the subiculum.

Zeineh et al. (2003) argued that the differential encoding/retrieval responsivity of DG/$CA_{2/3}$ and subiculum, respectively, may challenge leading computational models of hippocampal function, which vest encoding and retrieval mechanisms within the same hippocampal subfields (O'Reilly and Rudy, 2001; Rolls, 1996). Other hr-fMRI data, however, are more broadly consistent with extant models, as encoding effects have been observed not

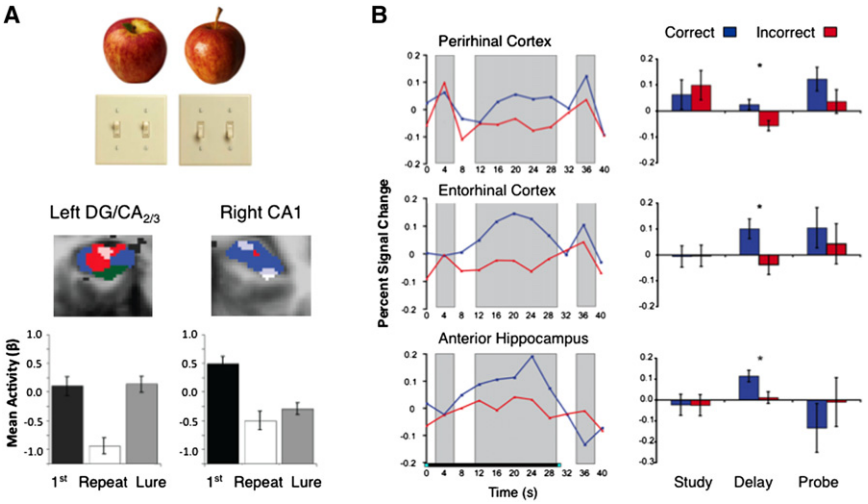

Figure 3. Pattern Separation and Delay-Period Activity

(A) Sample stimuli illustrating original and lure versions of objects. Activation clusters (white overlay) in DG/$CA_{2/3}$ (red) and CA_1 (blue) demonstrating biases toward pattern separation and completion, respectively. Bar graphs represent averaged activity extracted from each functional ROI in response to first presentation, repeat, and lure trials. This figure is modified from a figure in Bakker et al. (2008), with permission from AAAS.

(B) Time course activity extracted from anatomically defined regions of interest demonstrating delay period activity correlated with memory performance. Bar graphs depict mean signal change during study, delay, and probe. This figure is modified from a figure in Olsen et al. (2009), with permission from the Society for Neuroscience.

just in DG/$CA_{2/3}$, but in all subfields of the hippocampal circuit. For example, Suthana et al. (2009a) found significant performance-related CA_1 activity as participants learned to navigate a spatial environment independent of starting point and direction. Computational theories posit that during learning, CA_1 mediates the binding of CA_3 patterns with ERC representations, allowing CA_1 to serve as a "translator" during subsequent retrieval processes due to back-projections to ERC (e.g., O'Reilly and McClelland, 1994; Rolls and Kesner, 2006). Moreover, examining incidental encoding of faces and scenes, Preston et al. (2010) observed a significant novelty encoding effect (novel > repeated stimuli) in the subiculum and further showed that subicular encoding activity correlated with subsequent memory performance (Figure 2B). These findings complement related hr-fMRI observations of novelty encoding effects in human subiculum (Bakker et al., 2008; Zeineh et al., 2000) and argue against a restricted role of the subiculum in retrieval. Based on animal data, O'Mara (2006) proposed that the subiculum may be important in forming object-space associations by combining direct input from MTL cortical regions (including PRC) with input from the CA fields.

While additional data are clearly needed to better understand when encoding/retrieval functional dissociations are and are not obtained within the hippocampal circuit, we anticipate that hippocampal subfield function is not likely to be easily dichotomized according to the broad constructs of encoding and retrieval. Rather, increased mechanistic specificity is undoubtedly required to describe the underlying organizing principles of the hippocampus. As we next discuss, formal computational models of hippocampal function and empirical tests of these models in rodents and nonhuman primates offer a promising platform from which to formulate more specific hypotheses regarding functional differentiation in the human hippocampus.

Pattern Separation and Pattern Completion

The hippocampus is thought to support the rapid formation and subsequent retrieval of conjunctive memories that bind and reinstate the co-occurring elements of events (for a review, see Norman and O'Reilly, 2003). Guided by hippocampal anatomy and computational principles, neural-network models have formalized specific mechanisms by which hippocampal circuitry putatively mediates learning and remembering, namely the processes of *pattern separation*, *conjunctive encoding*, and *pattern completion* (McClelland and Goddard, 1996; O'Reilly and McClelland, 1994). Pattern separation refers to the transformation of overlapping patterns of cortical input into separable hippocampal representations and is posited to depend largely upon DG and its sparse connectivity with CA_3. Within CA_3, recurrent connections are thought to foster the building of multimodal conjunctive representations among coactive elements. Subsequently, when a partial cue is presented, CA_3 is thought to complete the encoded conjunctive pattern; this retrieved information then projects back to the cortex, via CA_1 and the subiculum, reinstating cortical patterns present during learning.

Consistent with these models, recent electrophysiological data from rodent hippocampus suggest that DG plays the clearest role in pattern separation, whereas both pattern separation and completion are performed to varying degrees by CA_3 and CA_1 (Guzowski et al., 2004; Lee et al., 2004; Leutgeb et al., 2004, 2007; Vazdarjanova and Guzowski, 2004). Specifically, in response to a parametric manipulation of pattern overlap, DG has been shown to exhibit greater differentiation when presented high pattern overlap than does CA_3 (Leutgeb et al., 2007). Studies examining differences between CA_3 and CA_1 further suggest that CA_3 responds in a nonlinear manner to pattern overlap, with low overlap triggering establishment of a novel hippocampal pattern (i.e., pattern separation) and higher overlap triggering establishment of a previously encoded pattern (i.e., pattern completion), whereas CA_1 responds more linearly (Guzowski et al., 2004; Lee et al., 2004; Leutgeb et al., 2004; Vazdarjanova and Guzowski, 2004). The conflicting tendency of CA_3 and CA_1 toward pattern separation or pattern completion, depending on the degree of overlap between past and present experience, further highlights the difficulty of classifying hippocampal subfield function according to singular constructs, such as encoding and retrieval.

Using hr-fMRI to determine whether differential biases toward pattern separation and completion are seen in human hippocampal subfields, Bakker et al. (2008) presented participants with a stream of visual objects that included objects presented for the first time (novel), identical repeats of previously presented objects (repeats), and novel objects that were similar to (e.g., were other exemplars of) previously presented objects (lures) (Figure 3A). Of interest was the degree to which each subfield displayed repetition suppression—that is, decreased activity relative to novel objects—for repeats and lures. Results revealed that DG/$CA_{2/3}$ activation was greater during both novel and lure trials relative to repeat trials, whereas activation in CA_1, and to a lesser extent subiculum, was greater during novel trials relative to both repeat and lure trials. Bakker et al. interpreted these findings to mean that DG/$CA_{2/3}$ is the principal hippocampal subfield biased toward pattern separation (because lures were putatively processed like novel events), whereas CA_1 and subiculum were biased toward pattern completion (lures were putatively processed like repeated events).

Bakker et al.'s data are the first to suggest functional heterogeneity within human hippocampus with respect to pattern separation and completion (for a potentially related hr-fMRI finding, see Johnson et al., 2008). Nevertheless, to better elucidate the relationship between input pattern overlap and hippocampal subfield responses, future studies will require a more systematic and quantitative manipulation of stimulus similarity. Such studies could then evaluate hypotheses regarding nonlinear (DG/$CA_{2/3}$) and linear (CA_1) subfield responses to pattern overlap, thus affording more precise comparisons to the rodent literature. While intriguing, it is also important to note that Bakker et al.'s (2008) results diverge from those described in a related hr-fMRI investigation (Kirwan and Stark, 2007), where far less conclusive findings of hippocampal subfield functional heterogeneity were reported despite using the same stimuli and similar stimulus conditions as in the Bakker et al. study. A potentially critical difference between these two experiments was the participants' retrieval orientation, with Kirwan and Stark requiring participants to make explicit judgments about the novel/repeat/lure status of stimuli, whereas mnemonic processing was incidental to the task in Bakker et al. Accordingly, task demands may influence the manner in which stimuli are processed by hippocampal subfields. Indeed, other recent data similarly suggest that automatic processes carried out by the hippocampus may be difficult to evaluate if participants adopt mnemonic strategies that alter hippocampal processing via top-down influences (Kumaran and Maguire, 2009; see also, Dudukovic and Wagner, 2007; Duncan et al., 2009). Because the interplay between goal states and hippocampal computation is currently poorly understood, future studies are needed to determine how choice of task influences hippocampal activity, the results from which will likely inform subsequent efforts to evaluate hippocampal subfield involvement in pattern separation and pattern completion.

More broadly, Bakker et al.'s investigation of pattern separation and completion processes in human hippocampal subfields is illustrative of how hr-fMRI can serve as a valuable tool in enabling comparisons between human and animal findings. Two recent hr-fMRI studies have similarly evaluated specific predictions about MTL subregion function advanced in the animal literature, with the first examining hippocampal subfield involvement in spatial navigation (Suthana et al., 2009a). In this study, the authors used hr-fMRI to evaluate MTL subfield activity as participants learned to virtually navigate a small town starting from either multiple start points (allocentric navigation) or the same start point (egocentric navigation). Results revealed greater activity in CA_1 for multiple than single start-point navigation (Figure 1B), as well as a correlation between CA_1 activity and behavioral performance in the multiple start-point condition. Such findings support data from rodents, suggesting a key role for the hippocampus in spatial navigation (for a review, see, e.g., Bird and Burgess, 2008) and for CA_1, in particular, in processing spatial relationships among landmarks (Goodrich-Hunsaker et al., 2008) and integrating novel spatial information with previously learned information (Vinogradova, 2001).

Inspired by electrophysiological findings of sustained, performance-related delay period activity in the rodent MTL during delayed-nonmatch-to-sample (DNMS) (Deadwyler and Hampson, 2004), and evidence that an intrinsically generated mechanism in ERC may support persistent activity (Egorov et al., 2002; Fransen et al., 2002), Olsen et al. (2009) used hr-fMRI to examine how human MTL subfield activity relates to trial-by-trial performance on a DMS task. Results revealed significant performance-related delay period activity in ERC, as well as in PRC and anterior hippocampus, across a 30 s retention interval, such that activity was higher for subsequently correct than incorrect trials (Figure 3B). In addition to complementing the electrophysiological findings in rodents, these hr-fMRI data build on rodent, non-human primate, and human lesion data implicating MTL in DMS and DNMS performance even at short delays (Hannula et al., 2006; Meunier et al., 1993; Meunier et al., 1996; Nichols et al., 2006; Olson et al., 2006a, 2006b; Suzuki et al., 1993; Van Cauter et al., 2008) and extend previous standard-resolution fMRI findings in humans (Nichols et al., 2006; Ranganath et al., 2005; Ranganath and D'Esposito, 2001; Schon et al., 2004) by providing precise functional localization and demonstrating a relationship between trial-by-trial variability in delay period MTL activity and immediate DMS performance. Collectively, the Bakker et al., Suthana et al., and Olsen et al. studies are illustrative of how hr-fMRI has begun to enable increased integration of human and animal data on MTL substructure function.

Hippocampal and MTL Cortical Representations

Beyond informing mechanistic accounts of hippocampal subfield function, hr-fMRI studies have begun to examine the nature of information representation in human hippocampus and surrounding MTL cortices. Several theories of MTL function suggest that PRC and PHC provide the hippocampus with information regarding the individual elements of an episode and the context in which they occur, respectively; the hippocampus is posited to then bind this information into a conjunctive memory of the event (for reviews, see Diana et al., 2007; Eichenbaum et al., 2007). Uncertainty remains, however, regarding the precise nature in which MTL subfields contribute to event memory. For example, PRC is often implicated in encoding and retrieving individual items (e.g., Davachi et al., 2003; Gonsalves et al., 2005; Henson et al., 2003; Montaldi et al., 2006;

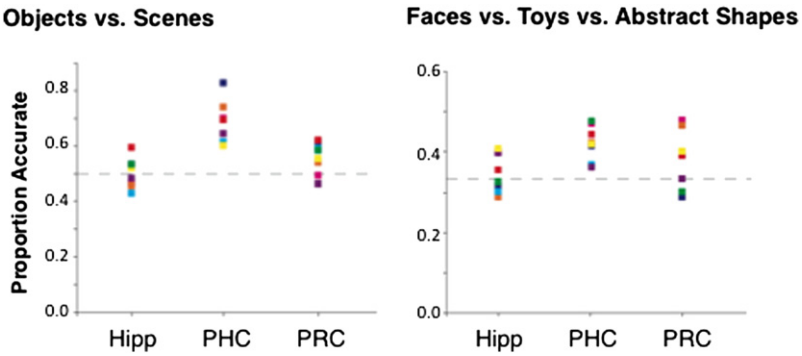

Figure 4. Multivariate Pattern Analysis in the MTL
Scattergrams depict the accuracy with which objects were differentiated from scenes (left) and different classes of objects from one another (right) in the hippocampus, PHC, and PRC using MVPA classifiers trained and tested on the data of individual participants (colored squares). Chance performance is indicated by the dashed line. This figure is modified from a figure in Diana et al. (2008), with permission from John Wiley and Sons.

Ranganath et al., 2004), yet several recent standard-resolution fMRI studies suggest that PRC may be capable of supporting certain forms of conjunctive memory, namely that between an item and its features (Haskins et al., 2008; Staresina and Davachi, 2006, 2008; Tendolkar et al., 2007). Extant data from PHC have proven to be similarly complex, with some evidence supporting a selective role of this region in processing spatial information (Epstein et al., 1999; Epstein and Kanwisher, 1998), but other data suggesting a broader role in representing spatial and non-spatial "contextual" information (Bar and Aminoff, 2003; Diana et al., 2007). An important caveat to many of these prior imaging studies is that they lack the resolution to unambiguously discriminate between PRC and ERC in the anterior parahippocampal gyrus; as a result, rostral cortical findings are sometimes cautiously localized (e.g., described as "anterior MTL cortex"; Henson et al., 2003). High-resolution imaging techniques allow for more precise delineation of boundaries between PRC, ERC, and PHC, as well as between these areas and the hippocampus. In this way, hr-fMRI provides increased anatomical precision as investigators attempt to elucidate the representational capabilities of MTL subregions.

An exciting new direction in understanding hippocampal and MTL cortical contributions to memory is the application of multivoxel pattern analyses (MVPA) to hr-fMRI data. Whereas univariate analyses focus on individual voxel activity in isolation or averaged activity across all voxels in an ROI, MVPA capitalizes on the rich information represented in spatially distributed activity patterns (Haxby et al., 2001; Haynes and Rees, 2006; Norman et al., 2006). Thus, the MVPA approach may be more sensitive than standard univariate approaches because MVPA can detect condition-specific changes in activation topography within a region, even when the mean activity in the region is indistinguishable across conditions (e.g., Harrison and Tong, 2009; Serences et al., 2009). However, if one were to perform MVPA on standard-resolution fMRI data from the MTL, classification performance might be hindered by the small number of voxels within each subregion; furthermore, the granularity of standard-resolution data may be too coarse to robustly detect information coding in the MTL. High-resolution MTL scans, capable of capturing more fine-grained activation patterns, may provide richer datasets for MVPA.

Two recent hr-fMRI studies have used an MVPA approach to shed light on categorical selectivity within the MTL cortex (Diana et al., 2008) and on the role of the hippocampus and surrounding cortices in spatial navigation (Hassabis et al., 2009). To characterize representational selectivity in MTL cortical regions and more specifically to assess whether PHC exhibits selectivity for spatial information, Diana et al. (2008) examined MTL activity patterns as participants viewed blocks of stimuli from five distinct categories (scenes, faces, objects, toys, and abstract shapes). Strikingly, MVPA revealed that patterns of activity within PHC contain sufficient information to decode which of the five categories a given participant was currently viewing, including above-chance classification between the nonscene categories (Figure 4). When these data were submitted to univariate analyses, however, only those contrasts involving scenes reached significance in PHC (see Preston et al., 2010, for related univariate hr-fMRI data revealing differential PHC responsiveness to scene versus face novelty and subsequent memory). In contrast to PHC, category information could not be reliably extracted from distributed activity patterns within PRC or the hippocampus, nor did univariate analyses reveal significant effects in these regions (see Preston et al., 2010, for hr-fMRI data demonstrating face and scene novelty and subsequent memory effects in PRC). Diana et al.'s findings are generally consistent with theories of MTL function positing that PHC can represent both spatial and nonspatial information (Diana et al., 2007; see also, Buffalo et al., 2006; Litman et al., 2009). While the behavioral significance of these distributed patterns of PHC activation have yet to be documented, Diana et al.'s (2008) data suggest that MVPA may be a fruitful method for characterizing MTL regional selectivity profiles.

In addition to its putative role in binding item and contextual details into an integrated conjunctive memory, the hippocampus is also posited to play a key role in spatial navigation (e.g., Bird and Burgess, 2008; Burgess et al., 2002). Motivated by findings of hippocampal place cells in rodents that show selectivity for specific environmental locations, Hassabis et al. (2009) used MVPA techniques to assess whether it is possible to predict an individual's location in a virtual reality environment based on distributed patterns of MTL activity. High-resolution fMRI data were collected as participants navigated two unique rooms, each consisting of four target positions. Rather than evaluate activity patterns in predefined MTL subfields, Hassabis et al. used a searchlight approach (Kriegeskorte et al., 2006) to evaluate spherical cliques of voxels within a bounding box surrounding the MTL. Searchlight MVPA revealed activation clusters within the posterior hippocampus that supported above-chance classification of an individual's location within a room and activation clusters within PHC that supported differentiation between the two rooms. Univariate analyses, on the other

hand, failed to reveal activity differences associated with specific locations or rooms. Hassabis et al. suggest that the ability of the hippocampus to discriminate individual locations within a room may form the basis of an allocentric cognitive map representing the room's layout (in agreement with Suthana et al., 2009a), whereas PHC may extract contextual information from each room. The authors posit that their ability to predict a participant's location within a room using MVPA techniques may reflect hippocampal neuronal ensembles with predictable topographical functional organization—if neural codes were random and uniformly distributed across hippocampal voxels, classification of location would have been impossible. (It bears noting that hr-fMRI data submitted to flat-mapping analysis may not be well suited for searchlight MVPA because local patterns of activity among neighboring voxels may be disrupted as functional data are projected from 3D to 2D.)

In sum, while the behavioral relevance of distributed activity patterns within specific hippocampal subfields remains to be determined, the Diana et al. and Hassabis et al. studies highlight how successful application of MVPA techniques to hr-fMRI data sets can provide unique leverage on information representation within human MTL. Beyond representation, we anticipate that future progress in specifying MTL computations will also benefit from MVPA techniques. For example, efforts to measure pattern separation and pattern completion within the hippocampal circuit may be aided by the ability of MVPA to quantify the similarity of neural patterns, as MVPA could provide a continuous measure of the degree to which a particular representational construct is activated within DG/$CA_{2/3}$ and CA_1, thus affording a more precise estimate of putative sigmodial versus linear response profiles.

Challenges and Future Directions

Despite the promise of hr-fMRI for informing mechanistic and representational accounts of MTL substructure function, high-resolution functional imaging is not without its challenges. For example, the SNR of fMRI data diminishes proportionally to decreasing voxel size; thus, even with the gains afforded by reduced partial voluming (Bellgowan et al., 2006), high-resolution studies must often include more trials per condition and/or more participants to obtain statistically significant effects. In addition, the anterior extent of the MTL suffers from susceptibility artifacts due to proximity to bone and air-filled sinuses, leading to fMRI signal dropout in anterior parts of PRC and ERC and, to a lesser extent, anterior hippocampus (Ojemann et al., 1997; Schacter and Wagner, 1999). Thus, although these anterior-most regions can be differentiated anatomically, obtaining reliable functional signal from and observing differences between them can prove difficult. Fortunately, several approaches to this challenge exist, including (1) running an MTL-targeted high-order shim prior to collecting functional data to reduce B0 heterogeneity, (2) adopting pulse sequences that optimize signal acquisition from susceptibility-sensitive structures, such as spiral in/out protocols (e.g., Olsen et al., 2009; Preston et al., 2010), and (3) further increasing spatial resolution (e.g., by increasing the through-plane resolution to approach that of the in-plane resolution), which serves to decrease intravoxel spin dephasing in susceptibility-sensitive regions (e.g., collecting isotropic voxels; Bakker et al., 2008; Hassabis et al., 2009; Kirwan and Stark, 2007), though perhaps at an SNR cost for nonsusceptible regions.

Unfortunately, the physiological factors that give rise to signal dropout also result in signal displacement in the phase-encoding direction (Ojemann et al., 1997; Olman et al., 2009)—in the case of most high-resolution studies acquiring coronal images perpendicular to the long axis of the hippocampus, in the superior-inferior direction or vice-versa. The magnitude and form of displacements again depend on the particular functional sequence adopted, with EPI protocols being particularly prone to displacement. Although not always implemented in hr-fMRI studies, such displacement can be attenuated by collecting B0 field maps and subsequently correcting for the measured displacement. Several analysis software packages now include standardized tools for unwarping EPI images (e.g., FSL: http://www.fmrib.ox.ac.uk/fsl/fugue/feat_fieldmap.html; SPM: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), enabling future studies to more easily implement such corrections and benefit from increased precision in functional localization. Finally, signal displacement can be reduced by increasing image acquisition speed or reducing field of view in the phase-encoding direction, though at a cost of reduced SNR (Olman et al., 2009).

With respect to ROI analyses, a nontrivial factor in evaluating subfield function is the time required to manually trace multiple ROIs in both hemispheres. More importantly, issues pertaining to observer bias must also be considered, with the same observer ideally tracing all ROIs in a given study to maintain consistency across participants. Recent advances in automated segmentation of MTL subfields (e.g., Van Leemput et al., 2009) may reduce the need for manual demarcation of subfields and, thus, offer an associated reduction in both the time requirements and observer biases related to analyzing hr-fMRI data sets.

With respect to testing theories of hippocampal subfield function arising from computational models and animal studies, a major limitation of current hr-fMRI methodology is the difficulty in anatomically discriminating DG from $CA_{2/3}$. Despite the gains in resolution afforded by high-resolution imaging, segmentation of DG from $CA_{2/3}$ is difficult due to the relative absence of anatomical landmarks, particularly in anterior portions of the hippocampus. Recent advances in structural imaging techniques allow for segmentation of DG from $CA_{2/3}$ in a small number of slices (Ekstrom et al., 2009b). However, given that DG comprises a very small number of structural voxels, it is likely that, at the resolution of the functional images (often acquired at approximately three times lower resolution than that of structural data), many functional voxels will contain data from both DG and $CA_{2/3}$. To this end, further gains in functional resolution may be required for these regions to be reliably differentiated.

Further increases in functional resolution likely will facilitate other efforts to examine whether human MTL demonstrates functional heterogeneity within its subfields similar to that observed in the animal literature, such as the presence of parallel streams supporting the processing of spatial information (postrhinal, medial ERC, proximal CA1, distal subiculum) and nonspatial information (PRC, lateral ERC, distal CA1, proximal subiculum) (for a review, see Knierim et al., 2006). Given the rapid advances in parallel imaging technology, as well as the

increasing availability of 7T scanners, there is reason to be optimistic that hr-fMRI at 3T and higher fields will ultimately achieve the necessary enhanced functional resolution required to more fully integrate the human and animal literatures on MTL subfield function. It bears noting, however, that with gains in sensitivity afforded by higher field strength come increased dropout and distortion in anterior regions of the MTL (e.g., Krasnow et al., 2003; Krüger et al., 2001). Moreover, the effective resolution of hr-fMRI data ultimately will be constrained by the point-spread function of the BOLD response (Logothetis and Wandell, 2004).

A further challenge for relating hr-fMRI MTL subfield findings and recording data in animals is that, unlike direct single or multiunit recordings from the animal brain, the BOLD signal is thought to primarily reflect input and local neuronal processing from many thousands of neurons, rather than spiking/output activity (Angenstein et al., 2009; Logothetis et al., 2001; Logothetis and Wandell, 2004). Thus, hr-fMRI of the MTL may be too coarse to detect certain sparse coding properties of MTL neurons (e.g., grid cell responses in medial ERC), being better suited to comparisons with animal studies examining local field potentials (LFPs) or other measures of population activity. Furthermore, because fMRI is an indirect measure of neuronal function in which the BOLD signal peaks several seconds after neural response onset, the temporal resolution afforded is modest. As a result, hypotheses requiring knowledge of millisecond timing differences between regions, such as those regarding the order in which information flows through cortical and hippocampal circuitry, cannot be feasibly evaluated using fMRI alone. It is partly for this reason that a number of laboratories have begun to combine the high spatial resolution of structural and functional imaging with the high spatial and temporal resolution of direct intracranial recordings in human patients undergoing presurgical mapping for pharmacologically resistant temporal lobe epilepsy. While intracranial electroencephalography in patients is not widely available and the placement of electrode contacts is solely based on clinical necessity, extant data indicate that patients typically have multiple contacts throughout the MTL that can be effectively localized to specific subfields using high-resolution imaging (Ekstrom et al., 2008). In addition to addressing MTL function, efforts to integrate hr-fMRI, single-unit, and LFP data from patients can advance understanding of the relationship between MTL BOLD activity and direct neural responses (Ekstrom et al., 2009a).

Finally, a trade-off exists in collecting high-resolution images of the MTL in that only a limited number of high-resolution slices can be prescribed without exceeding a reasonable per-volume acquisition time (e.g., repetition times of 2–4 s). The tradeoff between volume coverage, spatial resolution, and temporal resolution typically results in slice prescriptions that exclude many brain areas outside the MTL and its immediate surroundings. This restricted coverage prevents progress in understanding the functional connectivity between the MTL and regions outside the slice prescription. Replication of hr-fMRI experiments at standard resolution offer one means of assessing how extra-MTL regions, such as structures in prefrontal and parietal cortex, interact with the MTL.

Despite these challenges, hr-fMRI of the MTL is the first widely accessible technique to offer a window into the functional organization of the human hippocampus and surrounding cortices at the individual subfield level. Progress to date suggests that this approach may ultimately fulfill its promise to bridge the gap between functional neuroimaging in humans and electrophysiological, gene knockout and lesion studies in animals, as well as computational theories of the MTL. The extant hr-fMRI literature provides preliminary support for functional heterogeneity among human MTL subfields and offers a springboard from which future studies can address specific hypotheses of subfield function motivated by the animal and computational literatures, as well as subfield involvement in psychological processes that are ideally measured in humans, such as autobiographical recollection (e.g., Cabeza and St Jacques, 2007; Maguire, 2001) and future thinking (e.g., Schacter and Addis, 2009). High-resolution fMRI also offers an exciting means of evaluating MTL subfield activity in populations exhibiting memory impairments, such as older adults and individuals with dementia (Small et al., 2000a; Small et al., 2000b), those with genetic risk for Alzheimer's disease (Suthana et al., 2009b), and patients with schizophrenia (Gaisler-Salomon et al., 2009; Schobel et al., 2009) or depression. As researchers increasingly turn to hr-fMRI to advance understanding of human MTL function, the coming decade promises to bring substantial progress in specifying how our mnemonic lives depend on representations and computations within the MTL.

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