# 6

# Medial Temporal Lobe Subregional Function in Human Episodic Memory

## *Insights from High-Resolution fMRI*

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### Introduction

Episodic memory fundamentally shapes human behavior, allowing us to draw upon past experience to inform current decisions and make predictions about upcoming events. For decades, research has documented the critical role of the medial temporal lobe (MTL) in episodic memory (Eichenbaum and Cohen, 2001). While the link between MTL function and episodic memory is beyond debate, a recent focus has centered on characterizing the contributions of specific MTL substructures to episodic memory formation and retrieval (see Chapter 5).

The MTL (Figure 6.1a) comprises a heterogeneous group of structures, each with a unique cellular organization and pattern of anatomical connectivity. The subregions of the MTL include the hippocampus, which itself comprises the dentate gyrus (DG), the cornu ammonis (CA) fields, and the subiculum, as well as the surrounding entorhinal (ERC), perirhinal (PRC), and parahippocampal (PHC) cortices (Figure 6.1b). Several theoretical perspectives propose that anatomical differences between MTL subregions give rise to unique functional roles in episodic memory (Davachi, 2006; Diana, Yonelinas, and Ranganath, 2007; McClelland, McNaughton, and O'Reilly, 1995; O'Reilly and Rudy, 2001). However, testing how MTL subregions contribute to human memory function poses a unique challenge for cognitive neuroscience research. Individuals with MTL lesions typically have damage that affects several MTL subregions, spanning both hippocampus and surrounding MTL cortices. Even those individuals with restricted hippocampal lesions have damage to multiple hippocampal subregions. Therefore, while the neuropsychological study of MTL patients has taught us a great deal about the essential nature of the region for episodic memory, it is limited in its ability to discern the functional roles of individual human MTL subregions. Similarly, because MTL subregions are relatively small and adjacent, standard approaches to functional magnetic resonance imaging (fMRI) that use voxel dimensions greater than 3 mm cannot resolve signal originating from a particular MTL subfield. Testing

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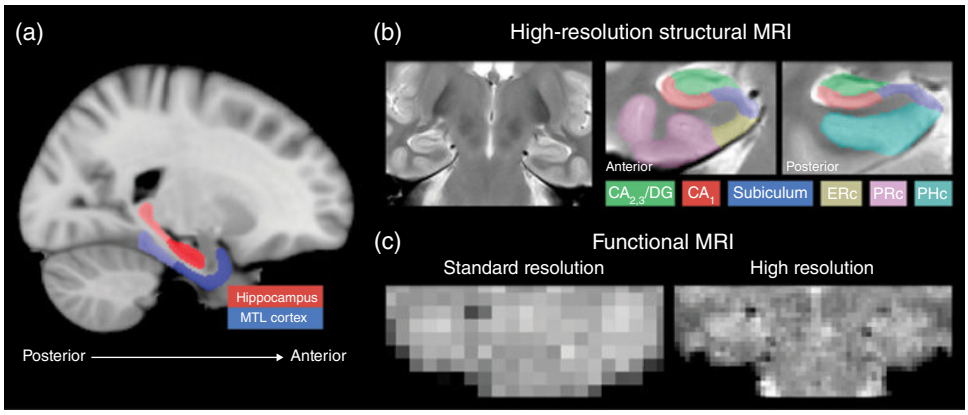


**Figure 6.1** High-resolution fMRI of human MTL subregions. (a) Sagittal brain slice depicting the location of the hippocampus (in red) and surrounding MTL cortex (in blue). Dark gradation indicates the anterior portions of the hippocampus and MTL cortex, while light gradation depicts the corresponding posterior regions. (b) Structural images collected using high-resolution MRI in the coronal plane, perpendicular to the anterior–posterior MTL axis. Anterior and posterior segments show demarcation of anatomical MTL regions of interest (ROIs) including hippocampal subfields DG/CA2/CA3, CA1, and subiculum and MTL cortical subregions ERC, PRC and PHC. (c) Left panel shows a standard-resolution fMRI image acquired using a functional sequence (3.75 × 3.75 × 3.6 mm voxels); right panel shows a high-resolution fMRI image acquired using a GRAPPA-EPI sequence (1.5 mm isotropic voxels).

the predictions of anatomically based models of MTL function in the human brain thus requires a spatial resolution beyond the limits of neuropsychological study and standard functional neuroimaging methods.

Over the last decade, implementation of high-resolution functional magnetic resonance imaging (hr-fMRI) has opened the door for investigation of MTL subregional function in humans. In this chapter, we review the technical aspects of hr-fMRI as applied to the study of the human MTL and discuss two core topics that have dominated research in this area: (1) functional dissociations between hippocampus and surrounding MTL cortices based on episodic memory content, and (2) functional distinctions between the components of the hippocampal circuit. We also discuss new multivariate pattern-information analysis techniques, which examine distributed patterns of activation in contrast to average responses pooled across an entire region. Such techniques, when combined with hr-fMRI, have the power to provide new insights into the function of MTL subregions. We end by discussing challenges for hr-fMRI of the human MTL and suggest future directions that could improve our ability to answer questions about the role of this region in episodic memory.

## What is High Resolution When it Comes to Human MTL Imaging?

Standard fMRI methods typically employ inplane resolutions of $\geq 3 \times 3$ mm (Figure 6.1c). At this spatial resolution, precise identification of distinct hippocampal subfields is not possible, and the ability to differentiate activation arising from the ERC and PRC is also limited. A little over a decade ago, two research groups

(Small *et al.*, 2000a, 2000b; Zeineh, Engel, and Bookheimer, 2000) developed techniques that enabled data acquisition from human MTL with enhanced spatial resolution ($< 2 \times 2$ mm inplane resolution) that when combined with specialized data analysis procedures afford localization of blood-oxygen-level-dependent (BOLD) signals to individual MTL subregions (Figure 6.1c). Such reduced voxel sizes not only improve the ability to distinguish anatomical boundaries between regions, but also reduce partial volume effects that may mask activations of interest (Bellgowan *et al.*, 2006).

These initial studies, and several that followed them, acquired functional images in the oblique coronal plane (inplane), perpendicular to the long axis of the hippocampus, with a larger voxel dimension in the anterior–posterior direction (thruplane; e.g., $1.6 \times 3 \times 1.6$ mm; Zeineh, Engel, and Bookheimer, 2000). By increasing spatial resolution in the coronal plane, these methods maximize the ability to identify key anatomical landmarks (Amaral and Insausti, 1990; Duvernoy, 1998; Insausti *et al.*, 1998; Pruessner *et al.*, 2000, 2002) that distinguish the boundaries between MTL subregions in the human brain. More recent studies (Bakker *et al.*, 2008; Hassabis *et al.*, 2009) have advanced acquisition methods further, allowing for isotropic voxel dimensions at the resolution of 1.5 $mm^3$. In all cases, hr-fMRI methods enable segmentation of the human hippocampus into the subiculum, CA1, and a combined DG/CA2/CA3 region (these subfields cannot be accurately differentiated even using current hr-fMRI methods; Figure 6.1b). These high-resolution acquisition techniques also afford more accurate segmentation of parahippocampal gyrus into the ERC, PRC, and PHC subregions, and more recently have been used to differentiate medial and lateral regions within ERC (Schultz, Sommer, and Peters, 2012).

To preserve spatial resolution, hr-fMRI studies of MTL function typically forgo or apply only minimal smoothing, to minimize blurring of anatomical boundaries between regions. Several hr-fMRI studies have also refrained from conducting voxel-level group analyses, because of the inherent challenges of registering small MTL subregions across participants; instead, these studies employ anatomically based region-of-interest (ROI) analyses in the native space of individual participants. In this approach, the functional time-series is co-registered to an even higher-resolution structural image (e.g., $0.4 \times 3 \times 0.4$ mm) at the level of individual participants. Anatomical MTL subregions are then defined on the high-resolution structural image separately for each participant (Figure 6.1b), and task-related activation is extracted from each voxel within a region and averaged across all voxels in a given ROI. While this method avoids the potential issues of across-participant registration, it may also demonstrate reduced detection sensitivity, as voxels that are nonresponsive to the task are included in the averaging. To increase detection sensitivity, some studies first identify task-activated voxels within anatomical regions with a contrast orthogonal to the main question of interest and then perform selective averaging, assessing effects of interest on those task-activated voxels only. However, both of these ROI methods preclude detection of heterogeneous responses that may be present within individual MTL subregions, as an average response is calculated across all selected voxels in a region. If different voxels within a region have distinct response profiles, selective averaging further limits detection sensitivity.

In the past few years, several advances have been made in cross-participant registration techniques (Avants *et al.*, 2011; Ekstrom *et al.*, 2009; Yassa and Stark, 2009) that allow for reliable voxel-level analyses at the group level. These techniques employ fully

deformable nonlinear registration algorithms to warp each participant's anatomical and functional images to a template image (either a target participant's brain or a study-specific group template) using each participant's anatomically defined MTL subregions as a guide. After cross-participant registration, second-level group analyses can be used to identify activation patterns that are consistent across the group. One previously successful approach to cross-participant analyses relies on computational unfolding of MTL images into two-dimensional flat maps (Ekstrom *et al.*, 2009; Zeineh *et al.*, 2003). However, the unfolding operation can be prone to error that results in large spatial distortions, leading to inaccurate labeling of subregions after warping. Label-guided alignment approaches result in more accurate correspondence of MTL subregions across subjects and higher statistical sensitivity than standard methods (Yassa and Stark, 2009). Importantly, these methods also permit visualization of the topographic distribution of activation both within and across MTL subfields.

## Anatomically Derived Theories of MTL Subregional Function

Before delving into the empirical work using hr-fMRI to study human MTL function, it is important to consider the theoretical frameworks that guide such research. Leading models of MTL function in episodic memory (Davachi, 2006; Diana, Yonelinas, and Ranganath, 2007; Eichenbaum, Yonelinas, and Ranganath, 2007; Knierim, Lee, and Hargreaves, 2006; Manns and Eichenbaum, 2006; McClelland, McNaughton, and O'Reilly, 1995; Norman and O'Reilly, 2003) derive many of their predictions from the anatomical organization of the region, with the putative function of each MTL subregion being linked to the nature of its inputs, outputs, and internal circuitry (Figure 6.2). In the case of MTL cortex, PRC receives predominant input from unimodal visual association areas in ventral temporal cortex, while PHC receives input from posterior visual association areas in parietal cortex as well as auditory and somatosensory information (Jones and Powell, 1970; Suzuki and Amaral, 1994; Van Hoesen and Pandya, 1975; Van Hoesen, Pandya, and Butters, 1975). This pattern of extrinsic connectivity with neocortex suggests that episodic memory encoding and retrieval may differentially recruit PRC and PHC depending on the nature of event content, with PRC supporting memory for visual objects and PHC supporting memory for visuospatial information. An influential extension of this view suggests that PRC mediates memory for individual items experienced within single episodes (the "what"), while PHC mediates memory for the context in which those items were experienced (the "where") (Davachi, 2006; Diana, Yonelinas, and Ranganath, 2007; Eichenbaum, Yonelinas, and Ranganath, 2007).

Moreover, PRC and PHC provide the respective inputs to the lateral and medial ERC in the rodent brain (Figure 6.2, dark blue arrows) (Burwell, 2000; Van Hoesen and Pandya, 1975), suggesting that the segregation of mnemonic content would also be reflected in different regions of the ERC (Knierim, Lee, and Hargreaves, 2006; Manns and Eichenbaum, 2006). While PRC and PHC projections remain segregated within ERC, parallel inputs from lateral and medial ERC converge onto the same subsets of DG granule cells and CA3 pyramidal cells in the rodent hippocampus (Figure 6.2, light blue arrows) (Canto, Wouterlood, and Witter, 2008). DG in turn

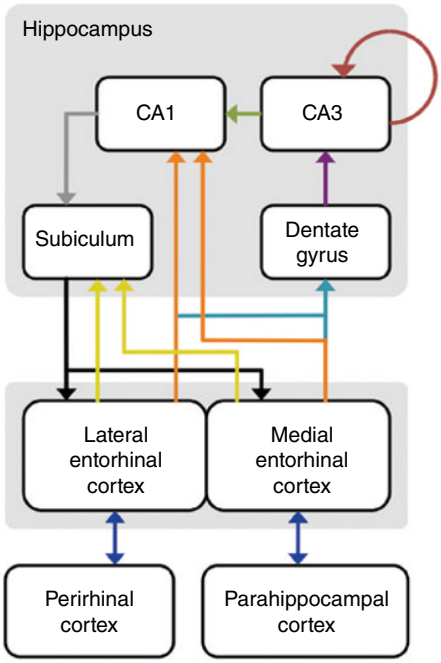


**Figure 6.2** Schematic diagram of connectivity between MTL cortex and hippocampal subfields. See text for detailed description of circuitry. Although not pictured, subiculum also receives direct input from PRC and PHC.

projects to CA3 via the mossy fiber pathway (Figure 6.2, purple arrow) (Witter *et al.*, 2000). Projections from CA3 pyramidal cells include collaterals to other CA3 pyramidal cells comprising an extensive system of associational connections within the region (Figure 6.2, brown arrow). The convergence of inputs from lateral and medial ERC, as well as CA3 collateral connections, potentially distinguishes the putative function of the DG and CA3 from that of MTL cortical regions, with these hippocampal regions playing a domain-general role in episodic memory by binding disparate inputs from PRC and PHC into cohesive memory representations for long-term storage, i.e., binding the "what" happened to the "where" it happened (Diana, Yonelinas, and Ranganath, 2007; Eichenbaum *et al.*, 2007).

Whereas mnemonic processing in MTL cortical regions would be distinguished by their selective responses to specific forms of event content, hippocampal memory traces would reflect the arbitrary relationships among multimodal event elements as well as associations between those elements and the context of their occurrence ("what happened where") (Eichenbaum and Cohen, 2001; Morris *et al.*, 2003). Importantly, the sparse connectivity between DG and CA3 is thought to magnify distinctions between overlapping patterns of cortical input elicited by highly similar events, a process termed *pattern separation* (McClelland, McNaughton and O'Reilly, 1995; O'Reilly and Rudy, 2001). Pattern separation is thought to result in separable memory traces for highly similar events that reduce the likelihood that memories would interfere with one another. CA3 circuitry is also hypothesized to support reactivation of stored memories from partial cues through recurrent excitation, a processed termed

*pattern completion* (McClelland, McNaughton and O'Reilly, 1995; O'Reilly and Rudy, 2001). While DG and CA3 likely make distinct contributions to pattern separation and pattern completion, hr-fMRI methods to date have not reliably distinguished between either of these subfields or between the adjacent CA2 region. Thus, the majority of hr-fMRI studies commonly define a single region that encompasses all these structures, which is typically referred to as DG/CA2/CA3.

Further along in the hippocampal circuit, CA3 provides a major input to CA1 (Figure 6.2, green arrow), which also receives direct input from ERC (Figure 6.2, orange arrows). Notably, whereas the projections from lateral and medial ERC converge on the same cells in DG and CA3, they target distinct groups of cells in CA1 and subiculum (Canto, Wouterlood and Witter, 2008; Witter, Van Hoesen, and Amaral, 1989). The differences in ERC connectivity between hippocampal subfields suggests that while different forms of event content may evoke similar response patterns in DG and CA3, the responses of CA1 and subiculum may be heterogeneous with respect to different types of memory content, with different cells mediating memory for different kinds of content. Moreover, the convergence of inputs from CA3 and segregated sensory information from lateral and medial ERC in CA1 suggests that the CA1 hippocampal subregion compares memory-based output from CA3 pattern completion mechanisms to incoming sensory information from ERC to detect deviations between current events and stored memories (Hasselmo and Schnell, 1994; Kumaran and Maguire, 2007; Lisman and Otmakhova, 2001; Vinogradova, 2001). When current experience violates expectations cued from memory, this CA1 comparator mechanism is thought to drive new encoding processes that form a new memory trace or update existing memories to account for new information.

The subiculum, the final structure in the hippocampal circuit, receives highly processed input from CA1 (Figure 6.2, gray arrow) as well as direct inputs from ERC (Figure 6.2, gold arrows), PRC, and PHC. As the output structure of the hippocampus, the role of subiculum may be to distribute highly processed input from the CA fields to the neocortical regions from which the input originated (Kloosterman, Witter, and Van Haeften, 2003). For example, information about reinstated memories resulting from CA3 pattern completion would reach the subiculum via CA1; via back-projections to PRC and PHC (Figure 6.2, black arrows), subiculum could then facilitate reinstatement of the content-specific neocortical patterns active during initial learning. It is important to note that much of what we know about the structure and connectivity of the MTL region is based on the rodent brain, in particular the distinction between medial and lateral ERC, and it remains to be seen whether such distinctions translate to the human brain.

In addition to these hypothesized functional differences between hippocampal subfields, there has been renewed interest in functional differences along the anterior–posterior axis of the hippocampus (Poppenk *et al.*, 2013). Animal research has shown that the anatomical connectivity and function of the ventral (anterior in the human) and dorsal (posterior in the human) hippocampus are distinct. In the rodent brain, the higher density of neuromodulatory inputs to ventral hippocampus relative to the dorsal hippocampus (Gage and Thompson, 1980; Verney *et al.*, 1985) suggests that this region represents the behavioral salience of incoming information to guide memory formation regardless of content type (Fanselow and Dong, 2010; Moser and Moser, 1998). In contrast, animal lesion studies suggest that posterior hippocampus may be selectively involved in spatial learning tasks (Moser, Moser, and Andersen, 1993;

Moser *et al.*, 1995). Episodic memory representations in the human brain might also reflect such anatomical and functional differences along the anterior–posterior hippocampal axis, with the posterior hippocampus playing a predominant role in mediating memory for information about the spatial context of individual events.

Collectively, these anatomical considerations provide an important theoretical framework motivating the body of studies using hr-fMRI to study human MTL function. In each of the following sections, we consider how hr-fMRI has informed these influential theories of MTL subregional function, beginning with empirical work on content representation in the human MTL.

## Empirical Evidence for Content-Based Dissociations between Human MTL Subregions

Several neuropsychological (Barense *et al.*, 2005; Barense, Gaffan, and Graham, 2007; Bohbot *et al.*, 1998; Epstein *et al.*, 2001; Lee *et al.*, 2005a, 2005b) and standard-resolution neuroimaging studies in humans (Awipi and Davachi, 2008; Lee, Scahill, and Graham, 2008; Pihlajamaki *et al.*, 2004; Sommer *et al.*, 2005) have revealed functional differences between PRC and PHC along visual object and visuospatial domains respectively, as predicted by anatomically based theories (see also Chapter 10). However, other evidence suggests that processing of specific forms of event content is distributed across subregional boundaries. For instance, PRC responses have been observed during encoding of objects, faces, and scenes (Buffalo, Bellgowan, and Martin, 2006) and during binding of items to their specific features (Haskins *et al.*, 2008; Staresina and Davachi, 2006, 2008). Similarly, mnemonic responses in PHC have also been demonstrated for multiple forms of event content including spatial and nonspatial contextual information (Aminoff, Gronau, and Bar, 2007; Bar and Aminoff, 2003; Bar, Aminoff, and Ishai, 2008; Litman, Awipi, and Davachi, 2009).

These findings thus suggest two distinct possibilities for the nature of content representation in PRC and PHC: one consisting of well-defined PRC and PHC functional modules exhibiting preferential responding to specific event content, and an alternative possibility with PRC and PHC processing and representing multiple forms of event content. High-resolution fMRI provides additional empirical leverage to distinguish between these opposing possibilities by enabling more precise delineation of the boundaries between MTL cortical regions – in particular PRC from ERC – as well as unambiguous discrimination between MTL cortex and hippocampus.

Similarly, by delineating activation patterns arising from individual hippocampal subregions, hr-fMRI may resolve conflicting views of hippocampal function that alternately suggest processing in this region is either content-general (Awipi and Davachi, 2008; Davachi, 2006; Diana, Yonelinas, and Ranganath, 2007; Knierim, Lee, and Hargreaves, 2006; Manns and Eichenbaum, 2006; Staresina and Davachi, 2008) or specialized for spatial memory (Bird and Burgess, 2008; Kumaran and Maguire, 2005; Taylor, Henson, and Graham, 2007). One intriguing possibility suggested by the anatomical data is that distinct hippocampal regions, either individual subregions or different regions along the anterior–posterior hippocampal axis, may show dissociable response patterns with respect to representation of different forms of event content.

In an initial hr-fMRI study examining content-sensitivity in MTL regions (Preston *et al.*, 2010), participants performed an incidental target detection task during the presentation of trial-unique, novel face and scene stimuli intermixed with highly familiar faces and scenes. Consistent with its proposed role in visuospatial processing, PHC responses were greater for novel scene trials relative to novel face trials. Moreover, greater activation in PHC scene-selective voxels was associated with enhanced subsequent scene memory. In contrast, PRC showed a pattern of novelty-based responding that was similar for faces and scenes. Moreover, the magnitude of novelty-based responses in face-sensitive and scene-sensitive voxels in PRC and subiculum correlated with later memory performance for each respective form of event content. While these findings are consistent with a content-specific role for PHC in episodic encoding, they suggest that mnemonic processes in PRC and subiculum are generalized across different forms of event content (see also Dudukovic *et al.*, 2011).

Notably, exploration of content-sensitive responses in ERC was limited in these initial hr-fMRI reports, with minimal task-related activation observed in either study. Animal work suggests, however, that ERC plays a key role in episodic encoding and retrieval, with the lateral ERC mediating memory for object-related information and the medial ERC mediating spatial memory (Knierim, Lee, and Hargreaves, 2006; Manns and Eichenbaum, 2006). Recent hr-fMRI work has examined these hypothesized dissociations in content representation between the lateral and medial ERC, finding enhanced modulation of lateral ERC activation during face retrieval, in contrast to enhanced medial ERC activation during the retrieval of spatial information.

New perspectives on content representation in the MTL have arisen from the application of multivariate pattern-information analyses to hr-fMRI data. Standard univariate fMRI analyses compare the mean response of a group of contiguous voxels across experimental conditions to isolate individual voxels or regions that show a statistically significant response to the experimental conditions of interest. To increase statistical sensitivity, univariate approaches may include spatial averaging across multiple voxels (e.g., a mean response to faces and a mean response to scenes within a specific anatomical ROI, as illustrated by the bar chart in Figure 6.3a). Although this approach reduces noise inherent in all fMRI acquisitions, it also reduces sensitivity by blurring out fine-grained spatial patterns that might discriminate between experimental conditions (Kriegeskorte and Bandetti, 2007). Instead, multivariate pattern-information approaches enhance detection sensitivity by looking at the contribution of multiple voxels, treating the pattern of response across all voxels within a region as a combinatorial code related to distinct mental operations (e.g., encoding faces versus encoding scenes; see Chapters 1 and 2 for more discussion of multivariate pattern-information techniques).

One such technique is multi-voxel pattern analysis (MVPA; Haynes and Rees, 2006; Norman *et al.*, 2006). Whereas univariate approaches use multiple regression to predict the activity of individual voxels based on the experimental condition, classification-based MVPA uses multiple regression to predict the experimental condition based on the activity of multiple voxels. In this approach, a machine-learning algorithm called a neural classifier is trained to distinguish brain patterns based on condition (e.g., whether the participant is encoding a face or a scene) using a subset of data. The trained classifier is then tested on previously unseen data (Figure 6.3b). Only if the experimental conditions are represented by distinct spatial patterns will final classifier predictions be accurate.

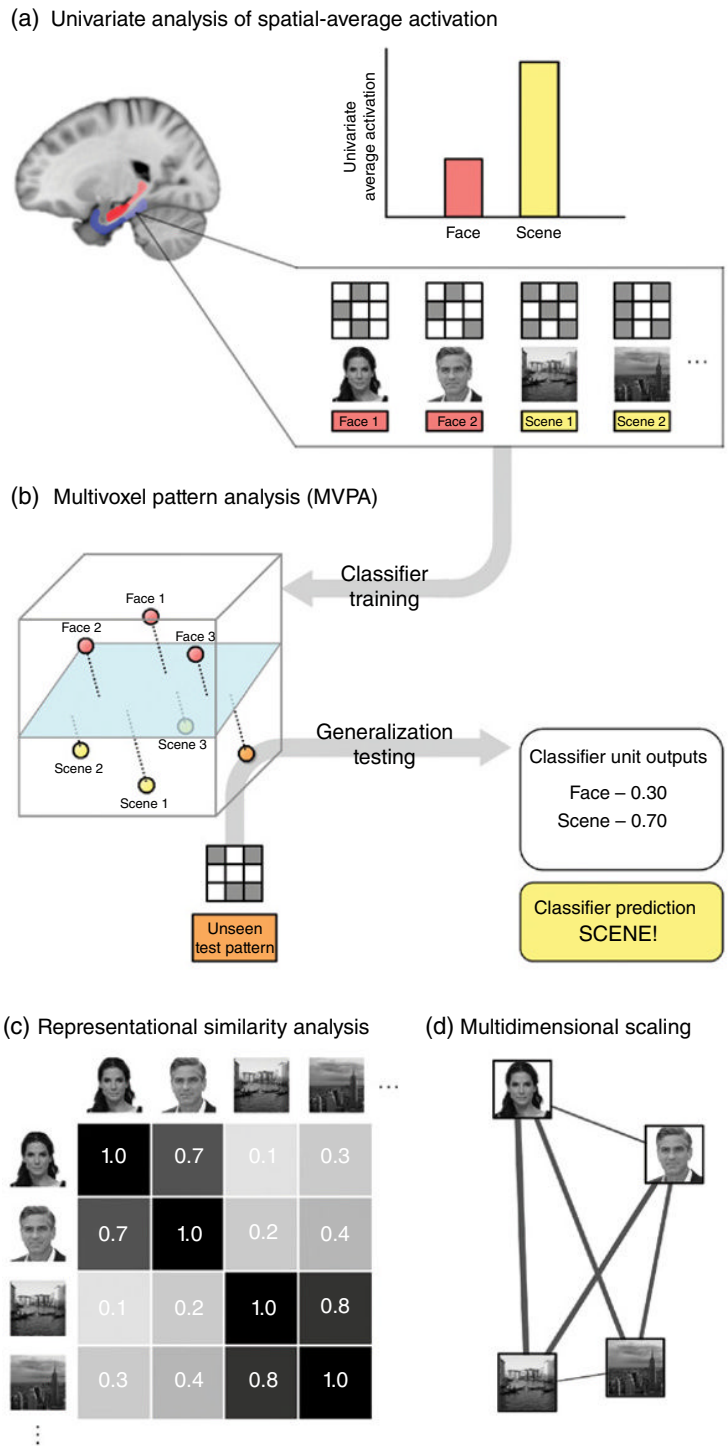


**Figure 6.3** Univariate and multivariate approaches for fMRI analysis. While standard univariate analyses (a) average across multiple voxels, multivariate approaches consider the contribution of multiple voxels, examining the pattern of response across all voxels within a region. Multivariate approaches include multi-voxel pattern analysis (b) and representational similarity analysis (c), the latter which makes use of multidimensional scaling (d).

A related approach is representational similarity analysis (RSA; Kriegeskorte and Bandettini, 2007; Kriegeskorte, Mur and Bandettini, 2008) which does not use neural classifiers but rather examines the similarity structure (through correlation) between the multi-voxel patterns elicited by experimental conditions (Figure 6.3c). RSA assumes that if two stimuli (e.g., two different faces) are represented similarly in the brain, there should be enhanced similarity between the multi-voxel patterns evoked by the two stimuli (i.e., a higher correlation value). Conversely, distinct mental representations would be reflected by dissimilar multi-voxel patterns. Representational similarity matrices can be visualized using multidimensional scaling (MDS), where stimuli evoking similar voxel patterns are plotted closer together in representational space, while stimuli evoking dissimilar voxel patterns are plotted further apart (Figure 6.3d).

To date, two hr-fMRI studies have employed MVPA methods to examine content-based differences in MTL subregional representation. In the first study (Diana, Yonelinas, and Ranganath, 2008), participants viewed images in blocks composed of different forms of visual content (objects, scenes, faces, toys, and abstract shapes). While patterns of activation in PRC and hippocampus did not contain sufficient information to classify the different content types, PHC demonstrated accurate classification performance across all stimulus types tha included visual objects and faces. However, univariate analyses of PHC responses revealed a selective response to scenes. These findings highlight that univariate and multivariate approaches to fMRI data analyses index different aspects of the neural code, and further indicate that the scene-selectivity of PHC responses observed in previous studies, both standard- and high-resolution, do not convey the full nature of content representation in PHC.

A second hr-fMRI study (Liang, Wagner, and Preston, 2012) extended this work by demonstrating robust coding of many forms of event content in both PRC and PHC using both MVPA and RSA. In this study, participants incidentally encoded visual (faces, scenes, visual words) and auditory (environmental sounds, spoken words) stimuli. As in prior research, the univariate response in PRC was maximal for faces, while PHC showed a scene-selective pattern of response. However, these PRC and PHC effects were accompanied by greater consistency between multi-voxel patterns evoked by faces and scenes in both regions, and in the case of PHC, auditory stimuli as well. Importantly, the distinct representation of face, scene, and auditory content in PHC was most prominent at the most posterior aspect, counter to the prediction from standard-resolution univariate analyses (e.g., Epstein and Kanwisher, 1998; Staresina, Duncan, and Davachi, 2011) that this posterior aspect should be the most scene-selective region of PHC. Moreover, the distinctive representation of faces and auditory content was observed in PHC despite the absence of an above-baseline response for these stimuli in the univariate analyses, further emphasizing the enhanced sensitivity of multivariate methods to representational content in MTL regions.

Liang, Wagner, and Preston (2012) also observed different patterns of content-based responding across the anterior–posterior axis of the hippocampus. Mean univariate responses in anterior hippocampus were above baseline for all content classes. However, the spatial pattern of response in this region did not discriminate between different forms of event content. In contrast, posterior hippocampus showed a distributed coding of scene content that was distinct from other forms of content. These findings are consistent with the anatomically based view that anterior and posterior hippocampus serve different functions with respect to episodic memory. Anterior hippocampal signals may convey the behavioral salience of stimuli (e.g., that a stimulus is novel or rewarding)

regardless of the perceptual form of the stimulus, while posterior hippocampus may play a predominant role in representing spatial memory content (see also Hassabis *et al.*, 2009).

Another means of assessing MTL content representation is to assess how specific regions within the MTL communicate with one another – a method known as *functional connectivity* (see also Chapter 13). Recent hr-fMRI studies indexing connectivity within the MTL circuit provide convergent evidence for functional differences along the anterior–posterior hippocampal axis, particularly in CA1 and subiculum (Libby *et al.*, 2012). This work revealed that anterior regions of CA1 and subiculum show predominant connectivity with PRC regions, while posterior CA1 and subiculum show greater connectivity to PHC. Such differences in anterior–posterior hippocampal connectivity with cortex were notably absent in the DG/CA2/CA3. These findings provide the first evidence that, in the human brain, PRC and PHC communicate with distinct regions of CA1 and subiculum, whereas PRC and PHC communicate with DG/CA2/CA3 in a similar manner. In particular, these connectivity findings suggest that distinct coding of spatial content in posterior hippocampus observed using MVPA approaches (Hassabis *et al.*, 2009; Liang, Wagner, and Preston, 2012) may primarily reflect CA1 and subiculum representations derived from PHC input.

One issue surrounding high-resolution MVPA studies of MTL content representation (Diana, Yonelinas, and Ranganath, 2008; Hassabis *et al.*, 2009; Liang, Wagner, and Preston, 2012) is the lack of a direct link between distributed patterns of activation and behavioral measures of memory performance. It is therefore unclear whether the distributed representations of event content observed in PRC, PHC, and posterior hippocampus observed in these studies are related to successful encoding of specific types of stimuli. Recent hr-fMRI evidence suggests that distributed hippocampal activation patterns distinguish individual episodic memories during vivid recall (Chadwick *et al.*, 2010; Chadwick, Hassabis, and Maguire, 2011). Moreover, patterns of hippocampal activation elicited by individual complex scenes have been used to decode participants' choice behavior in a perceptual decision-making task (Bonnici *et al.*, 2012b), further linking distributed hippocampal representations to behavior. Future hr-fMRI work will be necessary to determine whether similar relationships between distributed MTL representations and memory performance are true for a diversity of event content beyond the spatial domain.

## Differentiation of Function between Hippocampal Subfields

In addition to providing key insights into the nature of content representation in the hippocampus and MTL cortex, hr-fMRI studies have played in important role in delineating the specific processes and computations that are supported by individual hippocampal subregions. To date, studies of hippocampal subregional function have focused on three core topics: (1) the differential role of hippocampal subregions in encoding and retrieval processing, (2) hippocampal subregional computations that support pattern separation and pattern completion, and (3) the proposed comparator function of the CA1 field of the hippocampus.

## Hippocampal subregional contributions to episodic encoding and retrieval

One of the earliest hr-fMRI studies of the MTL demonstrated a dissociation of encoding and retrieval operations between hippocampal subfields (Zeineh *et al.*, 2003). While DG/CA2/CA3 was engaged during encoding of face–name pairs, subiculum was engaged during retrieval of learned associations (Figure 6.4a). Similarly, several follow-up studies found that DG/CA2/CA3 encoding responses were greater for remembered than for forgotten events (Eldridge *et al.*, 2005; Suthana *et al.* 2009, 2011) even when memory was tested after a long delay (Carr *et al.*, 2010). In contrast, responses in CA1 and subiculum were associated with success effects at the time of retrieval (Eldridge *et al.*, 2005; Viskontas *et al.*, 2009). Based on these findings, the authors hypothesized that the input structures of the hippocampus, DG/CA2/CA3,

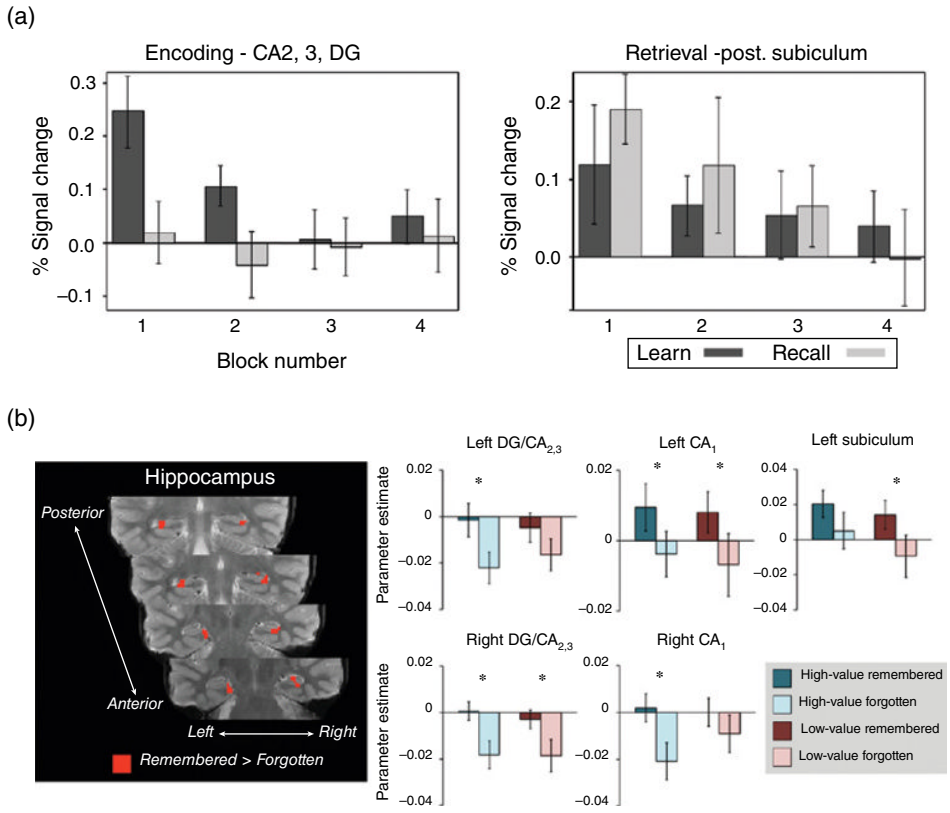


**Figure 6.4** Encoding and retrieval effects in hippocampal subfields. (a) Encoding- and retrieval-related activation in hippocampus for face–name paired associates. Percent signal change is plotted for each of four alternating encoding and recall blocks in DG/CA2/CA3 (left) and posterior subiculum (right). Adapted with permission from Zeineh *et al.* (2003). (b) Encoding activation in hippocampus during paired associate encoding under conditions of high and low reward. Voxels within the hippocampus demonstrating subsequent memory effects are displayed in red (left). Bar graphs (right) depict encoding activation in DG/CA2/CA3, CA1, and subiculum for high-value remembered trials (dark blue), high-value forgotten trials (light blue), low-value remembered trials (red), and low-value forgotten pairs (pink). Adapted with permission from Wolosin, Zeithamova, and Preston (2012).

are predominantly engaged during new event encoding, whereas the output structures of the hippocampus, the CA1 and subiculum, subserve the successful retrieval of memories (see Olsen *et al.*, 2009, for supporting evidence from a delayed-match-to-sample paradigm).

However, in contrast to these studies, anatomical models of hippocampal function emphasize that individual subfields play important roles during both encoding and retrieval and may transiently switch between states (Colgin *et al.*, 2009; Hasselmo and Schnell, 1994; Hasselmo, Schnell, and Barkai, 1995; Meeter, Murre, and Talamini, 2004). Indeed, other hr-fMRI studies have shown encoding and retrieval processes that are localized to multiple hippocampal subfields. During incidental encoding, subiculum activation was modulated by the novelty of the presented item (Bakker *et al.*, 2008), with the degree of novelty-related modulation predicting later memory (Preston *et al.*, 2010). Furthermore, an hr-fMRI study examining the effect of reward on encoding responses in MTL subregions found that encoding activation was related to later memory in all hippocampal subfields (Figure 6.4b; Wolosin, Zeithamova, and Preston, 2012). Similarly, several studies have shown retrieval success effects throughout the hippocampal circuit (Chen *et al.*, 2011; Suzuki, Johnson, and Rugg, 2011). Together, these recent experiments illustrate that encoding and retrieval processes are not restricted to specific hippocampal subfields as suggested by earlier studies. However, further work is required to determine whether subfields might perform specific aspects of encoding and retrieval, such as encoding of the environment during spatial navigation (Suthana *et al.*, 2009) or of salience cues encountered during novel events (Wolosin, Zeithamova and Preston, 2012).

## Pattern separation and completion

Another central focus of hr-fMRI studies in humans has sought to characterize hippocampal subregional responses elicited by highly overlapping perceptual inputs to determine their putative roles in pattern separation and pattern completion. Convergent electrophysiological research in rodents has shown that DG responses exhibit the greatest differentiation between highly overlapping input patterns, indicating this region's key role in pattern separation (Leutgeb *et al.*, 2007). In turn, the role of CA3 and CA1 in pattern separation and pattern completion is thought to vary based on the degree of overlap between inputs representing past and present experiences, with the CA3 responding in a nonlinear manner to pattern overlap and the CA1 responding in a linear fashion (Guzowski, Knierim, and Moser, 2004; Lee, Rao, and Knierim, 2004; Leutgeb *et al.*, 2004; Vazdarjanova and Guzowski, 2004). For example, a low degree of overlap between input patterns leads to a novel pattern of response in CA3 (i.e., pattern separation), whereas higher degrees of overlap between input patterns elicits reinstatement of a previously established CA3 response (i.e., pattern completion).

In the first hr-fMRI study to demonstrate pattern separation and pattern completion biases in human hippocampal subfields (Bakker *et al.*, 2008), participants viewed a sequential presentation of visual objects that contained novel objects seen for the first time, identical repetitions of previously presented objects, and novel lure items that were perceptually similar to previously presented objects. This approach relies on an effect known as *repetition suppression*, in which MTL regions show a reduced BOLD response to previously viewed stimuli when they are later shown again. The authors

hypothesized that regions biased toward pattern completion would automatically reinstate the representation of a previously viewed object when presented with its corresponding perceptual lure, and thus show similar responses to both repeated and lure objects. In contrast, regions biased toward pattern separation would differentiate the lures from previously presented highly similar objects and treat them as novel, thus showing greater activation for both novel and lure trials relative to repeated objects. The results showed a pattern of activation in CA1 and subiculum consistent with pattern completion, whose response was reduced for both repeated and lure items. In contrast, responses in DG/CA2/CA3 showed a pattern separation bias, successfully differentiating lure trials from similar, familiar objects (for related hr-fMRI findings isolated to the entire hippocampal region see Johnson, Muftuler, and Rugg, 2008).

To address predictions from rodent models that the balance between pattern separation and completion in different hippocampal subregions may depend on the overlap between present input and past experience, a subsequent experiment used two types of perceptual lures that had either high or low degrees of perceptual similarity to previously presented objects (Lacy *et al.*, 2011). Consistent with prior findings, responses in DG/CA2/CA3 demonstrated a pattern separation bias, with the level of bias being similar for high- and low-similarity lures. In contrast, CA1 responses showed a graded response that depended on the degree of similarity between lures and familiar objects. These data converge with rodent research to suggest that human DG/CA2/CA3 shows a nonlinear response to overlapping patterns, while human CA1 responses are more linear in nature. However, future experiments that provide more quantitative manipulations of stimulus similarity across several levels of similarity will be required before making strong claims regarding the nature of pattern separation and completion biases in the human hippocampus. Notably, when the same stimuli and presentation procedures were combined with an intentional task focus, which required participants to identify each object as novel, repeated, or lure, dissociations between hippocampal subfields were not apparent (Kirwan and Stark, 2007). These divergent findings suggest that mnemonic demands have a major influence on processing in the hippocampus (see also Dudukovic and Wagner, 2007; Duncan, Curtis, and Davachi, 2009; Kumaran and Maguire, 2009), with task goals impacting the bias to form new memory representations versus retrieving existing ones. Future hr-fMRI studies are needed that directly address how goal states influence the computational properties of hippocampal subregions and, in particular, the trade-off between pattern separation and pattern completion.

One could also argue that paradigms manipulating visual similarity between individual objects as a means to study hippocampal pattern separation and completion biases do not assess the true nature of overlapping episodic memories. Using videos depicting real-world actions performed by individuals in different contexts, Chadwick *et al.* (2010) showed that the distributed pattern of hippocampal activation evoked during vivid recall distinguished between individual memories. However, because the episodes portrayed in the videos did not share common features, this study did not directly address how the hippocampus codes highly overlapping episodic memories. In a second study (Chadwick, Hassabis and Maguire, 2011), the videos were constructed from two realistic action sequences filmed on a "green screen" background that were superimposed on the same two spatial contexts, resulting in four video clips with highly overlapping features. Hippocampal activation patterns were distinct during recollection of each individual video, providing evidence for pattern-separated hippocampal representations depicting highly overlapping episodic information.

While these studies did not attempt to differentiate individual hippocampal subfields, the combination of these naturalistic stimuli, multivariate analysis methods, and quantitative manipulations of event similarity would be well suited to address critical questions of pattern separation and completion biases in individual MTL subregions. To date, only one published report has used multivariate classification to test for hippocampal subregional differences in pattern separation and completion biases, finding evidence for pattern completion in both CA1 and CA3 (Bonnici *et al.*, 2012a). Future high-resolution studies combining both univariate and multivariate methods will be necessary to determine how these results line up with prior work associating CA3 predominately with pattern separation.

## Hippocampus as a comparator

Several mnemonic processes, including pattern separation and pattern completion, require a comparison of the similarity between new events and existing memory representations. This comparator function is thought to elicit encoding processes when present events deviate from predictions derived from reinstated memory representations, and it has been hypothesized to rely on the CA1 subfield of the hippocampus (Hasselmo and Schnell, 1994; Kumaran and Maguire, 2007; Lisman and Otmakhova, 2001; Vinogradova, 2001). Two recent hr-fMRI studies (Chen *et al.*, 2011; Duncan *et al.*, 2012) tested this hypothesis by examining hippocampal subfield responses to memory probes that matched or did not match previously studied events. In one experiment (Chen *et al.*, 2011), participants studied associations between faces and houses prior to fMRI scanning. During the scanned retrieval phase, one member of the studied face–house pairs was presented at the beginning of the trial. During a delay period, participants were instructed to recall the stimulus paired with the cue image. At the end of the trial, participants judged whether a probe image was the correct paired associate (a match) or a familiar image from another studied face–house pair (a mismatch). For correctly judged probe items, CA1 showed greater activation for mismatch probes compared to match probe items, consistent with a comparator signal that detects deviations from cued expectations. However, this pattern of CA1 response was only observed for house probes that were preceded by face cues, suggesting that CA1 may specifically serve as a comparator in the spatial domain.

In a second study, participants studied three-dimensional room layouts prior to hr-fMRI scanning (Duncan *et al.*, 2012). During a scanned recognition phase, participants viewed studied rooms that contained changes in layout and/or pieces of furniture. Within the hippocampus, only CA1 responses demonstrated sensitivity to changes in studied images, with a graded pattern of response based on the number of changes. This graded pattern of CA1 response was observed irrespective of which dimension of change participants were instructed to pay attention to ("layout" or "furniture"), suggesting that the putative CA1 comparator response is automatic and does not depend on extrinsic task goals. While these studies provide compelling evidence that CA1 serves mnemonic comparator, further work is needed to determine how such automatic CA1 responses relate to successful encoding of new episodic information.

## Limitations and Future Directions for High-Resolution fMRI of Human MTL

While hr-fMRI has advantages over standard approaches to brain imaging, it does have limitations. Notably, many of the studies reviewed here employ coronal acquisitions with a large thruplane resolution (3 mm or more). Such acquisition parameters maximize resolution in the inplane direction, in which distinguishing anatomical landmarks are most evident, while minimizing repetition time. However, because the anatomical landmarks that define individual MTL subregions shift gradually along the anterior–posterior MTL axis, large thruplane dimensions may prevent precise localization of activation when voxels include signal from multiple subfields. For this reason, some hr-fMRI studies opt not to make strong claims about individual subfields, and prefer to treat the hippocampus as an entire region (e.g., Suzuki, Johnson and Rugg, 2011).

Current high-resolution methods are also limited in their ability to resolve CA2, CA3, and DG as separate regions, with virtually all current hr-fMRI studies treating these as a single region despite their dramatic differences in connectivity and structure. Recently, one hr-fMRI study reported functional differences between DG and other hippocampal subfields (Bonnici *et al.*, 2012a), made possible through structural acquisitions with higher thruplane resolution than previous studies (0.5 mm). While this procedure undoubtedly benefits from the use of anatomical landmarks visible only in the sagittal plane, some caution is warranted. First, the inplane resolution is somewhat lower than what has been reported in other hr-fMRI studies (0.53 versus 0.43 mm), thus losing detail in the plane most commonly used to segment hippocampal subfields. Second, the resolution of the underlying functional data (1.5 $mm^3$) is no different from prior studies, and thus the ability to distinguish signal arising from DG and each of the CA fields in the functional data remains unchanged. For this reason, strong claims about dissociable responses in DG and CA3, for example, likely cannot be made based on such data.

Finally, the effort to test theories concerning small substructures is hampered by signal dropout and geometric distortion in functional acquisitions that are not present in structural images. Such distortion and dropout is particularly evident in anterior MTL regions. Distortion increases the likelihood that signal will be errantly displaced from a hippocampal subfield to one of its neighbors. Although such distortion can be corrected using field maps, the low spatial resolution of standard field maps precludes correction of detailed structures such as the hippocampal subfields. Efforts are currently under way to integrate higher-resolution field maps into imaging analyses, but these maps require additional acquisition time and may provide limited benefits.

Recent technical developments, such as human 7 T imaging and multiband parallel imaging techniques (Moeller *et al.*, 2010), may further enhance spatial resolution, allowing us to move beyond current limitations. In particular, multiband parallel imaging techniques dramatically increase the number of slices that can be collected at a single time-point. Increasing spatial resolution beyond 1.5 $mm^3$ will enable finer distinctions between hippocampal subfields or subregions of ERC, while also providing more detailed patterns of activation that can be leveraged using multivariate analysis techniques. Lowering the sampling rate to 1 second (or less) will also provide richer datasets for functional connectivity analyses. Finally, these new acquisition techniques permit increased coverage beyond the MTL, while maintaining high spatial and temporal resolution, thus permitting novel investigations of how MTL subregions interact with memory centers in the frontal and parietal cortices.

## Concluding Remarks

High-resolution fMRI is an essential technique for evaluating theories of MTL function that had previously been tested only in animals. The combination of hr-fMRI and multivariate pattern-information analysis techniques, in particular, has substantially advanced our understanding of how memory is represented in MTL subregions, allowing for greater parity and convergence with animal studies. High-resolution fMRI techniques also have increasing translational relevance. Many of the paradigms described in this review are being applied to clinical populations with neurological and psychiatric disorders associated with memory impairment (e.g., Gaisler-Salomon *et al.*, 2009; Schobel *et al.*, 2009; Suthana *et al.*, 2009; Yassa *et al.*, 2010), providing further insight into the relationship between pathological changes to MTL subregions and disease processes that affect memory. New technical developments are likely to advance the field further, affording greater leverage to characterize the critical MTL computations and representations that underlie episodic memory.

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