Noninvasive Functional and Anatomical Imaging of the Human Medial Temporal Lobe

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The ability to remember life's events, and to leverage memory to guide behavior, defines who we are and is critical for everyday functioning. The neural mechanisms supporting such mnemonic experiences are multiprocess and multinetwork in nature, which creates challenges for studying them in humans and animals. Advances in noninvasive neuroimaging techniques have enabled the investigation of how specific neural structures and networks contribute to human memory at its many cognitive and mechanistic levels. In this review, we discuss how functional and anatomical imaging has provided novel insights into the types of information represented in, and the computations performed by, specific medial temporal lobe (MTL) regions, and we consider how interactions between the MTL and other cortical and subcortical structures influence what we learn and remember. By leveraging imaging, researchers have markedly advanced understanding of how the MTL subserves declarative memory and enables navigation of our physical and mental worlds.

One of the central aims of cognitive neuroscience research is to understand how human brain function relates to the mnemonic experiences that define much of who we are as individuals. Recent advances in noninvasive human neuroimaging have given rise to novel insights about the neural foundations of human memory, and have allowed neuroscientists to draw important connections between human and nonhuman animal research. Although noninvasive imaging techniques remain limited in their spatial resolution (we cannot yet describe the behavior of individual neurons in the human brain without implanting electrodes in patients undergoing brain surgery), they also have

important strengths that have allowed researchers to significantly advance mechanistic accounts of learning and memory. In this review, we begin with a historical perspective on noninvasive neuroimaging techniques and their application to the study of memory encoding. We then introduce more recent cutting-edge methodological approaches, as we discuss specific domains of memory theory that they have helped advance. Drawing on research examining the medial temporal lobe (MTL), we emphasize the power of such imaging techniques to allow scientists to make inferences about the types of mnemonic information represented by distinct brain areas, and to understand how the func-

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tions of different regions and neural networks underlie our ability to learn and remember the details of our lives.

Although it can be challenging to assay what nonverbal animals are thinking and why, working directly with humans allows researchers to directly probe the subjective experience of remembering in people, and to relate their cognition to underlying neural processes. For example, it is easy to ask a human participant about the contents of their memories, or to assay how confident they are about having previously encountered a stimulus. In this review, we document how the ability to relate behavioral indices of memory to measures of neural activity allows research to advance our thinking about the biological underpinnings of human cognition. We focus primarily on recent functional magnetic resonance imaging (fMRI), and anatomical magnetic resonance imaging (MRI) research addressing the role of MTL subregions in human declarative memory (principally, episodic memory for individual life events), and also highlight findings addressing how declarative memory mechanisms interact with those of procedural memory in service of efficient memory-guided behavior.

EPISODIC MEMORY ENCODING

In the course of a day, humans encounter a steady stream of sensations, emotions, thoughts, and actions elicited by the external world and internal states. Encoding mechanisms transform this stream of information into long-term neural representations of co-occurring event features—that is, into episodic memory traces—and, thus, establish lasting footprints in our minds of life's events.

Imaging and the Subsequent Memory Paradigm

How to noninvasively study memory-encoding processes in humans is not a trivial question. In healthy individuals, we cannot directly measure the synaptic and cellular dynamics that allow an experience to be encoded such that it can be later remembered. Instead, cognitive neuroscientists

have leveraged noninvasive imaging methods to identify neural correlates of memory formation in humans, evidenced as neural predictors of subsequent memory expression (Paller et al. 1987; Wagner et al. 1999; Paller and Wagner 2002; Spaniol et al. 2009; Uncapher and Wagner 2009; Kim 2011). Subsequent memory paradigms involve recording neural activity, using either electromagnetic or hemodynamic measures, while participants encounter and process stimuli (e.g., a series of words) during an “encoding period.” Subsequently, memory for each stimulus is tested after a delay, and encoding period activity is examined conditioned on the behavioral expressions of memory, such as whether the stimulus was subsequently remembered or forgotten, or remembered with high or low confidence. Differences in encoding period activity as a function of later memory outcomes, such as subsequently remembered and forgotten stimuli (termed “subsequent memory effects” or difference as a result of memory—“Dm”—effects), can then be interpreted in terms of their potential contributions to the formation of memories.

Early evidence for subsequent memory effects came from electroencephalography (EEG) research in humans (e.g., Sanquist et al. 1980; reviewed in Wagner et al. 1999). EEG is a non-invasive technique in which electrodes, placed on the scalp of a participant, passively record voltages at the surface of the scalp induced by ion currents in the underlying cortex (Niedermeyer and Lopes da Silva 2005). Because EEG signals reflect electrical current from neural activity, the temporal resolution of EEG is on the order of milliseconds, allowing researchers to address hypotheses about the time course of neural events. One of the most common ways to analyze EEG data is to study the profile of event-related potentials (ERPs), which are electrical responses time-locked to or evoked by the onset of a stimulus or response. By analyzing the averaged ERP time-course associated with stimulus encoding, Sanquist and colleagues (1980) provided initial evidence of a subsequent memory effect in humans, finding that items that were subsequently remembered had a more positive deflection in the ERP time-course

~450 to 750 msec after stimulus presentation (relative to items later forgotten).

Following this early finding, extensive EEG research corroborated the presence of multiple subsequent memory effects underlying successful encoding (e.g., Long et al. 2014; reviewed in Rugg 1995; Wagner et al. 1999; Friedman and Johnson 2000; Paller and Wagner 2002; Nyhus and Curran 2010). Among their discoveries, EEG studies showed that the encoding of memories is a multifaceted process characterized by no single neural response. Instead, this rich literature revealed that there are distinct electrophysiological signatures associated with encoding, which manifest both in different poststimulus time periods and different spatial locations on the scalp. Furthermore, distinct ERPs are associated with different types of subsequent memory, such as memory for specific stimuli versus the contextual details surrounding an encoding experience (Johnson et al. 1997; Bridger and Wilding 2010; Angel et al. 2013). Such data suggest that multiple neural structures and mechanisms underlie successful episodic encoding.

Although providing some leverage on the temporal dynamics of encoding activity, EEG data present an important challenge for understanding the neural bases of memory formation in humans. As a measure of electrical signal at the scalp, EEG is most sensitive to postsynaptic potentials generated in superficial layers of the cortex. Furthermore, the signals from millions of neurons in adjacent brain areas converge and are diffuse at the level of the scalp. As a result, although EEG provides excellent resolution about “when” a neural response happens, it is challenging to discern “where” this processing occurs. This limitation is less pronounced in fMRI, which suffers from low temporal resolution but affords spatial resolution at the millimeter scale. fMRI inherits these strengths and limitations from its use of oxygenated blood flow as an indirect measure of neural activity. The mechanistic link between the blood oxygen level-dependent (BOLD) fMRI signal and neural activity remains an active area of research (Logothetis and Wandell 2004). Most fMRI studies obtain data on the order of 3 to 4 mm³ resolution, and the technology is continually improv-

ing, with recent advances in MRI hardware and fMRI pulse sequences allowing for whole-brain imaging at substantially higher spatial and temporal resolution (Feinberg et al. 2010; Moeller et al. 2010). For example, acquisition and analysis techniques now allow for individual subject and group-level analyses of human brain activity at spatial resolutions approaching 1 mm (Zeineh et al. 2000; Grill-Spector et al. 2006; Ekstrom et al. 2009; Yassa and Stark 2009; Yassa et al. 2010), and in some cases even higher (Yacoub et al. 2008; Heidemann et al. 2012), positioning fMRI as a powerful tool for researchers to noninvasively pinpoint where activity related to memory, perception, and cognition occurs in the brain.

For memory researchers, this increased spatial resolution is particularly beneficial as it allows fine-grained investigation of functional distinctions within the human MTL (e.g., Kirwan et al. 2007; Bakker et al. 2008; Ekstrom et al. 2009; reviewed in Carr et al. 2010; Chadwick et al. 2011; Bonnici et al. 2012, 2013; Libby et al. 2012; LaRocque et al. 2013; Brown et al. 2014a). The MTL has long been understood to be critical for episodic memory, based on decades of research that was spurred by the landmark case of Henry Molaison (HM), whose ability to remember new experiences from his daily life was dramatically impaired following bilateral resection of the hippocampus, and portions of the neighboring MTL cortical structures (perirhinal, parahippocampal, and entorhinal cortex) (Scoville and Milner 1957; Corkin 2013; Squire and Zola-Morgan 1991; Squire and Zola-Morgan 1991; Squire and Zola-Morgan 1991). Although studies of HM and other patients suffering MTL lesions have yielded a multitude of novel insights about the role of the MTL in declarative memory (Eichenbaum and Cohen 2001; Squire et al. 2004; Moscovitch et al. 2006; Squire and Bayley 2007; Graham et al. 2010; Greenberg and Verfaellie 2010; Montaldi and Mayes 2010; Rosenbaum et al. 2014), a challenge for neuropsychological studies is to identify whether the observed memory deficits reflect impairments at encoding, retrieval, or both. Noninvasive human imaging techniques complement lesion studies, as they provide a critical set of tools for studying healthy brain function by measuring neural re-

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sponses at the time memories are encoded and, as we will later discuss, at the time that they are retrieved. Indeed, the first fMRI studies using the subsequent memory paradigm (Brewer et al. 1998; Wagner et al. 1998) provided early evidence that event-related levels of encoding period activation in the human MTL, as well as in the lateral prefrontal cortex, predict whether a stimulus will be later remembered or forgotten. We next consider how fMRI subsequent memory data have informed theory about MTL mnemonic function.

Testing Theories of MTL Functional Differentiation

Episodic memories often contain a remarkable wealth of detail from an object that caught our attention to the environment in which we encountered it. At retrieval, sometimes we only have a vague sense of recognition when viewing a previously encountered stimulus, whereas, at other times, we vividly recollect many details of the prior experience. A number of theoretical frameworks have been formulated in an effort to capture the link between this diversity in mnemonic experience and the functions of different subregions of the MTL, most notably the hippocampus, perirhinal cortex, and parahippocampal cortex (Cohen and Eichenbaum 1993; Murray and Bussey 1999; Brown and Aggleton 2001; Davachi 2006; Diana et al. 2007; Eichenbaum et al. 2007; Mayes et al. 2007; Graham et al. 2010).

Leveraging the subsequent memory paradigm combined with fMRI's ability to distinguish activity from distinct, but spatially proximal MTL cortical regions (Carr et al. 2010), researchers have begun to test competing hypotheses about how specific MTL subregions contribute to episodic memory. For example, fMRI studies have shown content specialization within the MTL cortex that is predictive of subsequent memory. Specifically, consistent with their differing connectivity with other cortical areas (Suzuki 2009), activity in the parahippocampal cortex at encoding has been shown to predict later memory for scenes, while activity in the perirhinal cortex at encoding predicts later memory for faces, objects (Litman et al.

2009; Preston et al. 2010; Staresina and Davachi 2010; Staresina et al. 2011), and their associations (Staresina and Davachi 2008; Watson et al. 2012). Convergent evidence suggests that such functional differentiation along the anterior–posterior axis of the MTL cortex is best understood as a continuous gradient; for example, Liang and colleagues (2013) showed that face/object and scene representations are coded to differing degrees across the MTL cortex, with the greatest specialization for scene memory in the posterior parahippocampal region and greatest specialization for face/object processing in the perirhinal cortex (see also Lee et al. 2008; Barense et al. 2010).

Although specific types of event content appear to be differentially represented along the anterior–posterior axis of the MTL cortex, the convergence of perirhinal and parahippocampal inputs on the hippocampus, via the entorhinal cortex, is thought to enable the binding of the distinct facets (i.e., “items” or “items and context”) of an event into a conjunctive memory trace. This theoretical perspective has garnered some support from fMRI subsequent memory studies, which have revealed that MTL cortical activity at encoding (principally in the perirhinal cortex) differentially predicts later item recognition memory, whereas hippocampal activity at encoding differentially predicts later memory for item–context and item–item associations (e.g., Davachi et al. 2003; Kirwan and Stark 2004; Ranganath et al. 2004).

Multivariate fMRI Analyses and Memory Theory

The high spatial resolution of MRI has recently been combined with multivariate analysis techniques (Norman et al. 2006; Kriegeskorte et al. 2008), providing a powerful new means to address the mechanisms giving rise to, and the representational contents of, episodic memories. One such technique—representational similarity analysis (RSA)—has been particularly informative for testing hypotheses about the neural mechanisms that support successful encoding. Briefly, RSA measures the similarity (correlation) between event- or stimulus-spe-

cific patterns of activation, which can be used to query how the similarity (or dissimilarity) of multivoxel patterns measured during encoding relate to subsequent memory. As we next illustrate, such measures provide important tests of theoretical predictions about MTL functional differentiation underlying memory.

One dominant theoretical perspective on the functional contributions of different MTL subregions to memory, the “complementary learning systems” model, holds that a hippocampal “pattern separation” mechanism supports memory for events by orthogonalizing (making more distinct) neural representations during encoding, allowing later retrieval cues to trigger memory for a unique event (O’Reilly and McClelland 1994; McClelland et al. 1995; O’Reilly and Rudy 2001; Norman and O’Reilly 2003; Norman 2010). Conversely, this perspective holds that the neighboring MTL cortex sup-

ports memory by gradually encoding neural representations that capture the commonalities across similar stimuli, permitting later item recognition on the basis of global similarity between the present and past. Using RSA, coupled with high-resolution fMRI of the MTL, La Rocque and colleagues (2013) computed the similarity of the multivoxel fMRI pattern elicited by a stimulus at encoding to the patterns elicited by other encoded stimuli. By computing these across-item pattern similarities for each MTL subregion—perirhinal cortex, parahippocampal cortex, and these researchers obtained strong support for the “complementary learning systems” framework: namely, greater across-item similarity in the MTL cortex, but reduced across-item similarity in the hippocampus, was predictive of later successful memory (Fig. 1).

RSA has also been used to gain leverage on a longstanding debate about whether the stabil-

Figure 1. Pattern similarity and separation in different medial temporal lobe (MTL) subregions supports encoding. (A) Anatomically defined hippocampus, perirhinal cortex, and parahippocampal cortex regions of interest, overlaid on a structural magnetic resonance imaging (MRI). (B) Across-stimuli representational similarity (within category, rw; across category, ra) was computed using Pearson correlations between the patterns of neural activity, across voxels, for pairs of stimuli. (C,D) Critically, logistic regression revealed that the similarity of an item's encoding pattern to those of other items in the perirhinal cortex (PRc) and parahippocampal cortex (PHc) positively predicted subsequent memory. Conversely, hippocampal (Hipp) pattern similarity negatively predicted subsequent memory. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$. (From LaRocque et al. 2013; adapted from several in the source, with permission, from the Society for Neuroscience © 2013.)

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ity of a neural representation across encoding experiences is beneficial for subsequent memory, or whether variability in the neural representations of a stimulus across experiences is beneficial (the “encoding-variability” hypothesis) (Martin 1968). In particular, RSA analyses of fMRI encoding data suggest that, in some contexts, representational stability may be beneficial to later remembering (Xue et al. 2010; Ward et al. 2013; but see Wagner et al. 2000), demonstrating that greater pattern similarity of an item’s neural representations across multiple encoding trials predicts better subsequent memory for the item. Although some questions remain (Xue et al. 2013; Davis et al. 2014), researchers are now positioned to measure, at the individual trial level and within an individual human brain, the large-scale distributed neural representations that underlie important aspects of memory behavior.

A related multivariate technique—multivoxel pattern analysis (MVPA)—has also been effectively leveraged to advance understanding of episodic memory, including testing the prediction that the “strength” of a neural representation at encoding predicts later memory expression. In MVPA, multivoxel activation patterns for two or more classes of stimuli (e.g., faces vs. scenes) are used to train a “classifier” to identify the characteristic activity patterns that maximally discriminate between the stimulus classes. As such, from training data, a classifier learns to partition neural patterns into class-labeled decision regions (e.g., patterns representative of faces and patterns representative of scenes), and then can be used to estimate where a novel test pattern falls with respect to the boundaries between these decision regions. Thus, when presented with a new test pattern, the classifier is used to predict to which of the learned classes the new event belongs (Norman et al. 2006; Rissman and Wagner 2012). Importantly, pattern classifiers can output probabilistic predictions about the new event’s likely class, which provides a trial-specific quantitative measure of the strength of neural evidence. Recently, researchers have shown that the “strength” of content-specific (i.e., face vs. scene) neural evidence in the visual cortex correlates with the magni-

tude of hippocampal univariate fMRI activity at encoding and, critically, predicts whether that information will later be remembered or forgotten (Kuhl et al. 2012; Gordon et al. 2013). These data suggest that the success of hippocampally mediated encoding of event details is influenced by, or at least covaries with, the strength or fidelity of the corresponding cortical representations. We expect that these, and other recent MVPA and RSA observations (Johnson et al. 2009; McDuff et al. 2009; Rissman et al. 2010; Ward et al. 2013), will be the first of many instances, in which the application of multivariate analytic techniques, combined with the spatial resolution of fMRI, allows researchers to make critical progress on open questions about the neurobiological mechanisms governing memory.

EPISODIC MEMORY RETRIEVAL

At its core, retrieval can be considered as the reinstatement or reconstruction of information that was encoded in memory (Dudai 2015). With the ability to measure large-scale neural networks involved in retrieval, researchers studying memory in humans are able to consider not only where features of encoded memories are “stored” in the brain, but which regions and processes contribute to what is successfully remembered (and in how much detail). In this section, we discuss noninvasive functional imaging findings that provide critical insights into (1) the role of MTL subregions at retrieval, and (2) how distributed neural networks can interact to guide goal-directed memory retrieval and memory-guided behavior.

Multivariate fMRI and Connectivity Analyses of Episodic Retrieval

As with encoding, multivariate pattern analyses provide a powerful approach to examine the expression of memory content at retrieval. For instance, early MVPA work from Polyn et al. (2005) showed that a classifier, trained to distinguish between neural patterns elicited by the encoding of face, object, and scene classes of stimuli, can predict which category of stimuli will be imminently freely recalled based on

shifts in these categorical neural patterns during retrieval. Other data indicate that the representational strength of face and scene patterns in the visual cortex during encoding is not only predictive of subsequent memory behavior, but also of the strength of pattern reinstatement at retrieval (Gordon et al. 2013), providing an important demonstration of the link between representations of experiences as they unfold and of memory for those experiences as they are retrieved.

Episodic memories are characterized by the representation of unique experiences in our lives. One strength of RSA for assessing episodic reinstatement lies in the ability to examine stimulus- or event-specific representations at retrieval. For instance, in a recent fMRI study, participants were presented with word–scene combinations during encoding and then, at retrieval, they were provided with only the word as a retrieval cue. It was found that stimulus-specific scene patterns were reactivated in the para-

hippocampal cortex when participants indicated they had recollected the target scene, but not when they indicated they had no recollection (Fig. 2) (Staresina et al. 2012; see also, Ritchey et al. 2008; Bosch et al. 2014). This is an important step toward demonstrating that episodic reinstatement in the MTL can be observed at the level of individual memory representations.

Although multivariate pattern analyses facilitate the study of representational content in specific brain regions, functional connectivity measures provide a means of noninvasively studying how different regions and networks interact in support of memory and cognition. Connectivity measures leverage variability in the magnitude and timing of fMRI responses across trials to index functional relationships between distinct regions (e.g., Friston et al. 1993, 2003; McIntosh and Gonzalez-Lima 1994; Cordes et al. 2000; Lowe et al. 2000; Greicius et al. 2003; Rissman et al. 2004; Sun et al. 2004; reviewed in Stephan and Friston 2010; Friston

Figure 2. Encoding period patterns in the medial temporal lobe (MTL) are reinstated during successful retrieval. (A) Anatomically defined hippocampus and parahippocampal cortex regions of interest, overlaid on a structural magnetic resonance imaging (MRI). (B) Representational similarity (Pearson correlation) in the parahippocampal cortex (PhC) showed that when word–scene stimulus pairs are successfully recollected, neural patterns at retrieval are significantly more similar to those elicited for the unique word–scene combinations during encoding than when only the word is remembered. These reinstatement measures were not present in the hippocampus (HIPP), but trial-by-trial hippocampal activity predicted reinstatement, consistent with pattern completion mechanisms supporting retrieval. ns, not significant; $*p < 0.05$. (From Staresina et al. 2012; reprinted, with permission, from the Society for Neuroscience 2012.)

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2011; Friston et al. 2013) and, within the context of memory, their relation to memory behavior. Such functional relationships can be either direct (i.e., activity in one region directly influences activity in the other) or indirect (i.e., mediated by the function of another region). The ability to study large-scale networks across the brain is a particular strength of noninvasive functional imaging measures in humans.

Connectivity measures provide an important means for studying how information is shared within the MTL system, and between the MTL and other networks in the brain. In the preceding section on encoding, we discussed how different features of memories, specifically object/item information and scene/spatial information, are differentially represented by the perirhinal and parahippocampal cortex, respectively. The integration of these signals via the hippocampus is theorized to be a key neurobiological step in episodic memory encoding, and provides a basis for stimuli to cue associated memories at retrieval (Marr 1971; Teyler and DiScenna 1986; Treves and Rolls 1994). For example, how is it that when we look at our desk lamp it can trigger a memory for the location where the lamp was purchased last week? Researchers have posited that this might occur via a systematic flow of information, whereby information about the lamp might elicit a spread of activity through associations in the hippocampus (known as “pattern completion”) that leads to reactivation of the other representations associated with the lamp. A recent development in functional connectivity approaches, known as effective connectivity, allows researchers to test evidence for such directional predictions about the flow of information in brain networks (McIntosh and Gonzalez-Lima 1994; Stephan and Friston 2010; Smith et al. 2011; Friston et al. 2013). Effective connectivity measures seek to support inferences about causality in connectivity, by modeling the fit of predicted directional relationships with an fMRI signal from a target network of brain regions. Using one form of effective connectivity, known as dynamic causal modeling (DCM) (Friston et al. 2003), researchers have provided evidence that retrieval of a memory from a cue arises from

information transfer within the MTL. Specifically, activity caused by processing a scene cue in the parahippocampal cortex can drive activity for an associated object in the perirhinal cortex, with this interaction being mediated by the hippocampus (Staresina et al. 2013). These data provide novel support for a fundamental prediction about the role of the hippocampus in mediating the link between segregated item or feature representations (here, scene and object information) in support of rich episodic remembering.

SPATIAL MEMORY AND THE CONTRIBUTIONS OF MULTIPLE MEMORY SYSTEMS

The functional interaction between separate spatial and nonspatial representations, mediated via the hippocampus, has important implications for the direction of future memory research. Although the early findings in patient HM provided a framework for decades of research on the role of the hippocampus in episodic memory, the existence of “place cells” in the rodent hippocampus (O’Keefe and Dostrovsky 1971; O’Keefe 1976; Moser et al. 2008, 2015) led to a separate hypothesis that the hippocampus creates internal “cognitive maps” of environments (Tolman 1948; O’Keefe and Nadel 1978). Although research examining the roles of the hippocampus in episodic and spatial memories increasingly crosses paths, these have historically remained two distinct areas of study in human cognitive neuroscience. One means of bridging the gap between these areas of research is to consider hippocampal representations of location as one mechanism underlying its broader role in associating stimuli and experiences across space and time (Eichenbaum and Cohen 2014).

In real-world scenarios, episodic memories encompass the “who, what, when, and where” of an experience and, thus, require the ability to embed nonspatial information (e.g., faces and objects) in memory for environments (e.g., Burgess et al. 2001; reviewed in Burgess et al. 2002; Bird and Burgess 2008). The effective connectivity data described in the preceding section

(Staresina et al. 2013) are an important step toward understanding how spatial and nonspatial memory signals combine within the hippocampus to support the expression (in addition to the encoding and construction) of such integrated knowledge. Moreover, recent high-resolution fMRI data show that, when scene information is presented as a cue for memory of a specific navigational episode, trial-by-trial responses in the parahippocampal cortex and the hippocampal CA1 subfield during cue processing correlate with prospective retrieval of the desired navigational event (Brown et al. 2014a). CA1 represents a final stage of processing in the hippocampal circuit, and theories of hippocampal function propose that the convergence in CA1 of representations from the CA3 subfield and the MTL cortex facilitates sequential retrieval, and gates hippocampal output to memories that are congruent with current context (Hasselmo and Wyble 1997; Hasselmo and Eichenbaum 2005; Kesner 2007). Brown and colleagues' high-resolution fMRI data, among other recent navigation work (Brown et al. 2010; Brown and Stern 2013), suggest that parahippocampal scene representations could underlie hippocampal reactivation of navigational episodes, and support key predictions about CA1's role in the flexible retrieval of goal-relevant memories. Moreover, complementary fMRI data (Suthana et al. 2009) have associated CA1 activity with the learning of allocentric (map level) representations of environments; such flexible spatial representations may be critical as a scaffold for remembering the locations of, and relationships between, specific events in our lives.

Building from the hypothesis that the hippocampus represents cognitive maps of environments, spatial navigation research has often contrasted hippocampal-dependent memory for complex spatial relationships between locations with navigation based on striatal-dependent motor associations for specific cues and landmarks (Hartley et al. 2003; Iaria et al. 2003; Doeller et al. 2008). Noninvasive measures of anatomical morphology have recently linked these concepts. Specifically, using one class of anatomical MRI analysis known as voxel-based morphometry (VBM) (Mechelli et al. 2005),

researchers have shown that volume estimates in the hippocampus and caudate nucleus differentially correlate with the predisposition of a person to rely on spatial knowledge or response-based strategies to solve navigational problems (Bohbot et al. 2007; Konishi and Bohbot 2013), as well as with the level of an individual's "expertise" as a spatial navigator (Maguire et al. 2006). Briefly, VBM leverages regional volumetric differences between anatomical MRI images for each participant and a standardized template brain. By examining the degree to which a brain region (e.g., hippocampus) must be enlarged or compressed to fit the template brain, researchers can infer volumetric differences between participants in their dataset. VBM analyses have been combined with automated methods for segmenting MRI images into gray matter structures (Fischl et al. 2002; Patenaude et al. 2011) to show that hippocampal volume predicts an individual's ability to learn and remember map-level information (Hartley and Harlow 2012; Schinazi et al. 2013) (such techniques have also been used with nonspatial memory paradigms to show functional specialization within the hippocampus—linking posterior hippocampal volume, specifically, with contextual memory performance [Poppenk and Moscovitch 2011]). Similarly, researchers have used diffusion tensor imaging (a method for tracking water molecule diffusion along white matter tracts in the brain) to show that greater directionality in water molecule diffusion in the hippocampus, putatively indicative of greater white matter integrity and organization, correlates with improved ability of participants to learn and retrieve cognitive map information (Iaria et al. 2008).

Critically, in the real world, we need a mechanism for flexibly translating both spatial and nonspatial forms of episodic memory into goal-directed actions. The hippocampus is not anatomically positioned to directly control motor behavior, and early evidence from rodent navigation studies (Devan and White 1999) led to the prediction that the hippocampus may direct behavior via engagement with striatal circuitry. Therefore, although hippocampal and striatal forms of memory may differ in fundamental ways (see Graybiel 2015), given that navigation-

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al memories are often complex and can incorporate both spatial and behavioral information, our ability to navigate in real-world settings may draw on both regions; more generally, integration of MTL and frontostriatal computations may be important for memory and memory-guided behavior in many scenarios as a function of their combined relevance to current task demands. The interplay between these systems can be compensatory; for example, fMRI research in Huntington's disease patients, who suffer from progressive pathology affecting striatal circuitry, has shown that route navigation—potentially supported by response associations in the striatum (Hartley et al. 2003)—can fall back on hippocampal computations as the striatal system fails (Voermans et al. 2004). Importantly, navigation of familiar routes in healthy populations can also rely on the hippocampus when navigational responses depend on explicit knowledge of the current navigational context, that is, when navigation draws more strongly on features of episodic memory.

A real-world example that most of us are familiar with is the experience of traversing an intersection between two familiar navigational routes. In this scenario, we need to choose between two possible directions based on memory for which path is most relevant to the goal of the current navigational episode. Consistent with the episodic memory demands of this scenario, recent VBM data show that hippocampal gray matter volume in young adults correlates with the ability to perform such context-dependent route navigation (Fig. 3A) (Brown et al. 2014b). Moreover, fMRI research has shown that people faced with alternative route memories in a virtual navigation task draw on both hippocampal and striatal processes to identify and select which path to take (Brown et al. 2010). In fact, not only do the hippocampus and the medial caudate (a striatal subregion implicated in behavioral flexibility) support learning of navigational episodes (Brown and Stern 2013), but their recruitment during navigation of familiar routes increases as memories for new alternative

Figure 3. Hippocampus and striatum support flexible navigational learning and memory. (A) Statistical map of bilateral hippocampal region, in which volume positively correlated with context-dependent route retrieval ability in healthy young adults (*upper frames*). Volume estimates extracted from the hippocampus tightly predict individual differences in performance (*lower frames*). (B) Navigation of familiar routes (overlapping [OL]_{old}; blue path on map) becomes increasingly reliant on hippocampal and striatal mechanisms as a novel interfering route memory is introduced (OL_{new}; green path on map)—fMRI activity in the left hippocampus and bilateral medial caudate increased from early to late navigation trials (blue line in graphs) as participants became more familiar with the novel competing route memory. In contrast, navigation of familiar nonoverlapping routes (nonoverlapping [NOL]_{old}; red line in graphs), for which contextual retrieval demands were limited, relied minimally on these medial temporal lobe (MTL) and striatal subregions from early to late trials (even decreasing for the medial caudate with continued practice). ROI, region of interest; VBM, voxel-based morphometry; R, right hemisphere; **p* < 0.05. (From Brown et al. 2014b and Brown and Stern 2013; adapted, with permission, from the authors.)

paths are introduced to the environment, increasing the need to draw on episodic memory to guide selection of behavior (Fig. 3B). Importantly, functional connectivity research suggests that the hippocampus and striatal circuitry interact cooperatively at retrieval when people need to use episodic memory to guide navigation (Brown et al. 2012). (Recent evidence also suggests that corecruitment of, and functional interactions between, the hippocampus and striatum may also be important in non-navigation settings for forming episodic memories [Ben-Yakov and Dudai 2011; Sadeh et al. 2011] and making episodic and relational memory judgments [Moses et al. 2010; Ross et al. 2011]). Furthermore, Brown and colleagues (2012) showed that the hippocampus and striatum functionally interact with regions of the prefrontal cortex during contextual navigation, suggesting that the prefrontal cortex may mediate goal-directed memory and the interaction between these systems. Ultimately, this line of research illustrates how episodic memory supported by the hippocampus plays a critical part in spatial navigation, and demonstrates that the distinct functions of the MTL and striatal systems can combine to support navigation in real-world scenarios in humans; more broadly, the imaging data described in this section have laid important groundwork for understanding (1) how we leverage multiple memory systems to achieve long-term goals, and (2) the importance of network interactions for constructing and navigating mnemonic representations of our lives.

CONCLUSIONS

The ability to remember an event from last week or to plan which route to take to the grocery store are fundamentally multiprocess and multinet network acts, integrating declarative memory with systems of attention, and cognitive and behavioral control. Noninvasive functional imaging techniques are essential for advancing memory neuroscience as a field, enabling the study of human memory at its many cognitive and mechanistic levels. These techniques have yielded novel insights into the types of information represented in distinct

brain regions, the mnemonic computations that specific regions perform, and how the functions of different regions interact to influence what we learn and remember about our world. Moreover, data addressing functional organization and neural network interactions from human research can serve as a crucial guide for directing neural recordings, invasive high-resolution imaging, and genetic and pharmacological manipulations in nonhuman animals. By leveraging these techniques to study how representational features, functional interactions, and anatomical morphology of brain areas support mnemonic experience, researchers will be able to better understand the neural basis of declarative memory and how changes associated with both development and disease affect this core element of the human condition.

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