Remembering Preservation in Hippocampal Amnesia

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Abstract

The lesion-deficit model dominates neuropsychology. This is unsurprising given powerful demonstrations that focal brain lesions can affect specific aspects of cognition. Nowhere is this more evident than in patients with bilateral hippocampal damage. In the past 60 years, the amnesia and other impairments exhibited by these patients have helped to delineate the functions of the hippocampus and shape the field of memory. We do not question the value of this approach. However, less prominent are the cognitive processes that remain intact following hippocampal lesions. Here, we collate the piecemeal reports of preservation of function following focal bilateral hippocampal damage, highlighting a wealth of information often veiled by the field's focus on deficits. We consider how a systematic understanding of what is preserved as well as what is lost could add an important layer of precision to models of memory and the hippocampus.

Contents

OVERVIEW

MTL: medial temporal lobe

Working memory: the transient holding online of information

Recognition memory: the ability to recognize previously encountered events, objects, or people

Familiarity: the feeling that an event was previously experienced, but without recollection of the associated details or context

Autobiographical memory: memory of our personal past experiences

Semantic memory: general and world knowledge

Memory is fundamental to everyday cognition. Consequently, a key goal of cognitive psychology and neuropsychology is to understand how memories are formed, represented, and recollected. Studies of patients with damage to a particular brain region, the hippocampus, have been pivotal in illuminating the organization of the memory system by showing, for example, that memory is not a unitary phenomenon. The importance of the hippocampus for memory was first formally demonstrated nearly 60 years ago by patient HM (Scoville & Milner 1957). Removal of HM's medial temporal lobe (MTL, which includes the hippocampi) for the relief of intractable seizures left him with profound amnesia, unable to recall any new personal experiences (episodic/autobiographical memories), and presurgical autobiographical memories were also compromised to a degree. Nevertheless, HM's cognition did not collapse; he retained an above-average IQ, apparently intact perceptual and language capabilities, and aspects of his memory—working memory and procedural learning—were also preserved. Furthermore, although elements of his recognition memory were impaired, his familiarity was not, and although his autobiographical memory was affected, his semantic memory for the same time periods was intact (Augustinack et al. 2014).

Scoville & Milner (1957) appreciated that HM's cognitive and memory profile had two equally important components—what was impaired and what was preserved—and that only by considering both could the structure of memory and its functional anatomy be properly understood. In the decades since the case of HM was first reported there has been a wealth of studies investigating patients with damage to the MTL, including those with focal lesions to the hippocampi (reviewed in Spiers et al. 2001, Winocur & Moscovitch 2011). However, this work has predominantly focused on patients' deficits. Indeed, even HM's purportedly preserved abilities have been questioned in recent years, with visual perception (Lee et al. 2012) and working memory (Ranganath & Blumenfeld 2005) reported to be impaired in patients with focal bilateral hippocampal damage. In other work, the remit of the hippocampus has been extended beyond autobiographical memory to include spatial navigation (Maguire et al. 1998, 2006; O'Keefe & Dostrovsky 1971; O'Keefe &

Nadel 1978) and imagining the future (Hassabis et al. 2007b), with deficits in these domains also apparent following hippocampal lesions.

Consequent upon the dominance of the lesion-deficit model in neuropsychology, consideration of preserved functions has been eclipsed by the field's emphasis on unearthing impairments. We believe this narrow focus could impede our ability to achieve a full understanding of hippocampal functionality and the organization of memory and related cognition. It is not that the field is devoid of evidence relating to the intact abilities of patients with hippocampal damage, but rather that what is there is piecemeal and has not been considered in its totality. Our main aim in this article is to redress the balance by collating some of the evidence that exists in the literature concerning preservation of function in the context of bilateral hippocampal damage. We then consider how a systematic understanding of what is preserved as well as what is lost could be used to inform a theoretically enriched understanding of memory and its neural substrates.

We focus primarily on patients with putative focal bilateral hippocampal damage. Where relevant, mention is made of animal work, patients with less focal hippocampal lesions, and functional magnetic resonance imaging (fMRI) studies.

WHY IS PRESERVATION PROBLEMATIC?

Before examining the pertinent empirical data, it is interesting to first consider why preservation has failed to achieve parity with reports of deficits in patients with bilateral hippocampal damage. As noted, neuropsychological research is traditionally based on the lesion-deficit model. The logic here is if a patient cannot do X, then the execution of X must depend upon the lesioned area. Investigations are therefore aimed at highlighting cognitive impairments following brain damage by finding statistically significant performance differences between patients and matched healthy participants, usually leading to conclusions about the necessity of a brain region for a specific task or function. Here preservation runs into its first problem. The usual analysis employed within psychology is that of null hypothesis significance testing. This test asks, at the simplest level, whether two means are different from each other. Finding a significant result (often with a threshold of $p < 0.05$—a deficit in function) lends itself to a simple conclusion—that the means of patients and control subjects are different. However, a nonsignificant or "null" result (typically $p > 0.05$—preservation of function) is not typically regarded as the reverse conclusion. Null results can occur for multiple reasons, for example, type II errors (accepting a false null hypothesis), low study power (the probability of correctly rejecting the null hypothesis when it is false), and poor experimental design.

Problems with preservation do not end there, as further issues arise in relation to interpreting the results. If, following hippocampal damage, some aspects of cognition are preserved, the simplest assumption is that the hippocampus is not required for those tasks to be performed. However, there are other potential explanations for preservation. First, brain structure and function are not fixed. Environmental stimulation or memory encoding can alter the structure of the brain; for example, when trainee taxi drivers learn the layout of ~25,000 streets around London, this is associated, within subjects, with increased gray matter volume in the posterior hippocampus (Woollett & Maguire 2011). Second, brain regions are not always selective in their responsivity—in the congenitally blind, visual areas have been found to activate during fMRI studies of braille reading (i.e., tactile inputs) and verbal memory (Amedi et al. 2003). As such, it is possible that following damage to the hippocampus, other brain regions may be able to compensate to some degree. This may be particularly relevant in developmental amnesia (Vargha-Khadem et al. 1997), where early life insult to the hippocampi may lead to a reorganization of function within the brain.

It is also uncertain to what extent remnant tissue contributes to cognitive tasks. It is typically assumed in neuropsychology that damage to brain structures of the extent usually observed in patients with hippocampal damage could in effect equate to a near-complete loss of functionality. That is, as stated by Gold & Squire (2005), "These observations suggest that a reduction in hippocampal volume of approximately 40%, as estimated from MRI scans, likely indicates the nearly complete loss of hippocampal neurons. The tissue collapses with the result that the hippocampus is markedly reduced in volume, but the tissue does not disappear entirely. Thus, a loss of approximately 40% of hippocampal volume as measured from MRI scans should not be taken to mean that 60% of the hippocampus remains functional" (pp. 84–85). However, several fMRI studies conducted with patients have shown that even where hippocampal tissue volume is reduced by 50%, it nevertheless activates during successful performance on tasks that are thought to be hippocampal dependent (e.g., Maguire et al. 2001, 2010a; Mullally et al. 2012a). Preservation may thus, in some cases, be supported by remnant portions of the hippocampus that are still functional.

People also differ in the strategies they employ to perform a task. These different cognitive styles and strategies can influence the brain networks engaged (Sanfratello et al. 2014), and this could be expressed in different patterns of preservation following brain damage. Further, the brain contains degeneracy; that is, many-to-one structure-function relationships (Price & Friston 2002). As such, and related to the use of different cognitive strategies and plasticity, preservation of function following lesions does not necessarily mean that the damaged region is never involved in a particular cognitive process.

So there is much to muddy the waters in preservation, and it is perhaps not surprising, therefore, that journal editors and individual scientists have long been wary of null results (Ferguson & Heene 2012, Rosenthal 1979) and concomitant conclusions regarding preservation of function. It should be noted that preserved performance on one task observed in the context of impaired performance on a second task within the same experimental design can temper some of the above concerns, although these single dissociations are not without their own interpretive issues (Dunn & Kirsner 2003).

DEFICITS ARE ALSO DIFFICULT

Studies investigating deficits are not, however, immune from problems either. They are also susceptible to type I errors (incorrect rejection of the null hypothesis) and poor experimental design. One of the most contentious issues is in relation to study power and sample size. It is often the case in neuropsychology that single patients are studied and compared to a small group of control subjects. This substantially raises the likelihood of type I errors and also makes it difficult to gauge the generalizability of findings. Discussion of these important issues is beyond the scope of this article, but see Rosenbaum et al. (2014) for recent consideration of these matters.

Beyond statistical issues, interpretation of deficits is not straightforward. In patients with bilateral hippocampal damage, the accusation is sometimes leveled that the lesions are not truly focal to the hippocampus and that damage to other areas might have contributed to the impairment, thus making conclusions specific to the hippocampus impossible (e.g., Kim et al. 2015, Squire et al. 2010). It has been further suggested that pathology arising from limbic encephalitis (LE) is invariably more diffuse compared with etiologies such as anoxia (Kim et al. 2015, Squire et al. 2010). However, postmortem studies of certain types of LE document highly selective hippocampal damage (Dunstan & Winer 2006, Khan et al. 2009, Park et al. 2007). On the other hand, patients who have been described as having selective hippocampal damage from non-LE pathologies can have wider brain damage (e.g., Kim et al. 2015: patient DA, heroin overdose, bilateral globus pallidus lesions; patient KE, toxic shock syndrome, basal ganglia lesions). We therefore

believe that arguments about the selectivity of lesions are specious because many pathological processes produce widespread brain damage, but only those rare patients with apparently selective hippocampal lesions are typically included in studies where the prime or sole interest is in the hippocampus (e.g., Mullally et al. 2012b).

Even where high-resolution MRI scanning of patients' brains has been undertaken and subsequent painstaking measurement of hippocampus and other regions confirm the circumscribed nature of the lesions, covert pathology that is undetectable using current technologies might be present. Indeed, even when a more remote brain area has not itself been directly damaged, diaschisis may have occurred—this is a sudden loss or change of function in a portion of the brain connected to a distant damaged brain area (e.g., Campo et al. 2012). For example, studies in rats using immediate-early gene imaging as a marker of neuronal activity found that lesions in the anterior thalamic nuclei and hippocampus both produce marked retrosplenial cortex (RSC) dysfunction (Albasser et al. 2007, Jenkins et al. 2004). This finding suggests that the functional impact of hippocampal lesions could be exacerbated by distal dysfunctions in RSC. These lesions had little or no effect on RSC cell numbers (Jenkins et al. 2004, Poirier & Aggleton 2009), so that seemingly intact cytoarchitecture (that might appear normal on an MRI scan) was combined with a functional abnormality. In humans also, focal brain lesions have been found to disrupt network organization across the brain during fMRI scanning (Gratton et al. 2012, Hayes et al. 2012).

The lesion-deficit model encourages conclusions about the necessity of a brain area for a specific function. But no brain region is an island, and so at best this is an oversimplification. Thus, even when strenuous efforts are made to confirm the circumscribed nature of hippocampal lesions in the context of a deficit (including subsequently at postmortem, e.g., Zola-Morgan et al. 1986), this must always be caveated by the possibility that the function in question may not be solely the domain of the hippocampus.

WHY BOTHER TESTING PATIENTS?

Given the difficulties outlined above, one might well question the usefulness of testing patients at all. We firmly believe in the value of neuropsychological research; it has been transformative for the field of memory and continues to hold its own even in these days of functional neuroimaging (Rorden & Karnath 2004). In fact, our aim in highlighting the issues faced by patient studies is to make the point that examining or theorizing about preservation is no more flawed or inappropriate than is postulating about deficits. Importantly, neuropsychology is constantly striving to improve its methods (for more on this, see Rosenbaum et al. 2014). For instance, complementing neuropsychological studies with fMRI in healthy control subjects helps to establish convergent evidence (e.g., Hassabis et al. 2007a,b). Similarly, conducting fMRI scanning on the patients themselves (during tasks they are able to perform) is becoming more common, and this can provide clues about the potential functionality of remnant tissue (Maguire et al. 2010a,b; Mullally et al. 2012a). Moreover, detailed statistical and methodological reporting can overcome some of the concerns associated with null results (see sidebar Interpretation of Null Results). The interpretation of deficits arising after bilateral hippocampal lesions has also benefitted from meta-analyses and in-depth reviews (Kessels et al. 2001, Spiers et al. 2001, Squire 1992, Winocur & Moscovitch 2011), which have included some consideration of preservation, specifically in the domain of learning (Cohen 1984, Schacter & Graf 1986). As far as we are aware, however, there have been no reviews of preservation of function across multiple domains.

Therefore, after a brief overview of hippocampal anatomy and extant theoretical frameworks, in the subsequent sections we consider a range of cognitive functions with which the hippocampus has been associated, starting with two of the classics, navigation and autobiographical memory.

INTERPRETATION OF NULL RESULTS

Although it is not statistically possible to accept the null hypothesis, meaningful conclusions can still be made from null findings. Interpretation does, however, require further reporting of the data, including effects sizes and confidence intervals as well as the usual p-values (e.g., Aberson 2002). Although this is recommended in the most recent edition (sixth) of the *Publication Manual of the American Psychological Association* (Am. Psychol. Assoc. 2010), it is not yet common practice. Effect sizes provide a standardized measure of the extent of the difference between two means (e.g., Cohen's *d*) or the proportion of variance explained (e.g., eta-squared or r^2). If effect sizes are very small, then differences between groups are likely to be nonsignificant even with greater experimental power. Confidence intervals around means and effect sizes measure the deviation around these variables—small confidence intervals that largely overlap suggest high similarity between groups; large confidence intervals or smaller regions of overlap suggest possible differences given greater sensitivity and power. Thus, more detailed description of the results, including where possible the data for each patient and every control subject, can increase the interpretability of the statistics leading to a null result.

Naturally we refer to deficits, but our prime focus is on highlighting those functions that seem to be completely intact as well as instances where pockets of preservation have been observed within the context of an overarching impairment. Although not exhaustive, this survey reveals some unexpected abilities, new angles on extant beliefs, and surprising gaps in our knowledge.

HIPPOCAMPAL ANATOMY

The hippocampus is a brain structure thought to be common to all mammals (West 1990) and is located in the MTL of each hemisphere (**Figure 1**). The hippocampal formation consists of two laminae rolled up inside each other. One formation is termed the hippocampus proper or *cornu ammonis*; it is subdivided according to differences in cellular structure into subfields named CA1, CA2, CA3, and CA4. The other lamina is the dentate gyrus. The entorhinal cortex mediates connections to and from the hippocampus; there are also direct connections between hippocampus and subcortical regions via the fornix. In rodents, the hippocampus runs along a dorsal-ventral axis, corresponding to a posterior-anterior axis in humans. Different parts of this axis have distinct connections to other regions of the brain, suggesting potential functional differentiation between dorsal and ventral hippocampus—an idea that receives support from a range of empirical data (e.g., Fanselow & Dong 2010, Maguire et al. 2000, Moser & Moser 1998, Poppenk et al. 2013, Strange et al. 2014).

The hippocampus in humans is susceptible to a range of common pathologies including Alzheimer's disease, epilepsy, limbic encephalitis, and stroke. The typical etiologies that gave rise to the focal bilateral hippocampal damage (as far as can be determined with current techniques) in the patients we consider here are anoxia, ischemia, and some forms of limbic encephalitis (**Figure 2**).

THEORIES OF HIPPOCAMPAL FUNCTION

An in-depth description of theories of hippocampal function is beyond the scope of this review, and these theories are amply covered elsewhere (Eichenbaum & Cohen 2014, Konkel & Cohen 2009, Maguire & Mullally 2013, O'Keefe & Nadel 1978, Squire & Zola-Morgan 1991). Here we

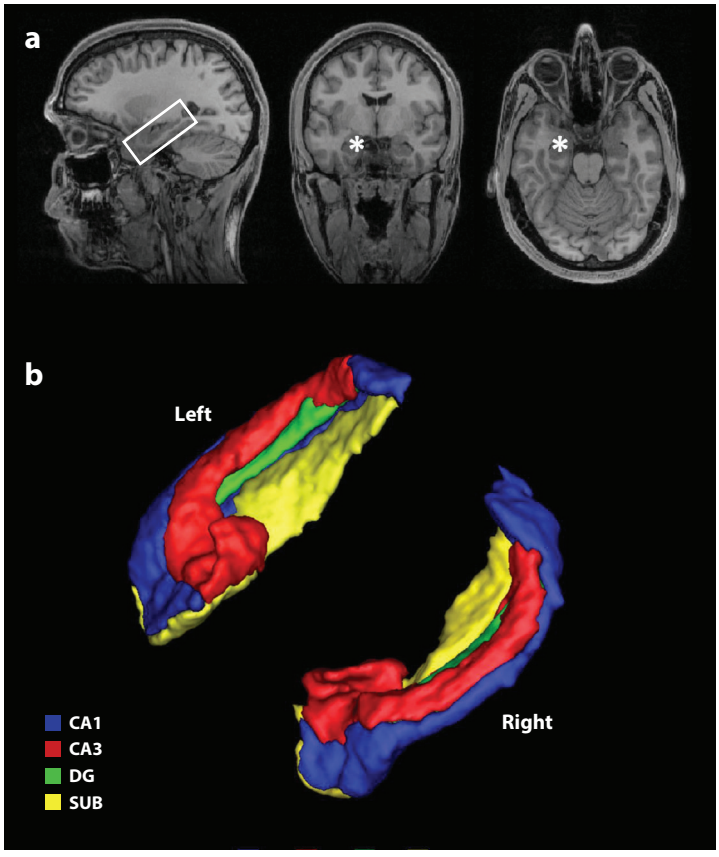

Figure 1

The anatomy of the human hippocampus. (*a*) The structural magnetic resonance imaging scan of a healthy individual in sagittal view (within the white box), coronal view, and axial view, where the left hippocampus is indicated with a white asterisk, and the right hippocampus is free to view. (*b*) A 3-D rendering of two hippocampi, with the subfields color-coded. Abbreviations: CA1, *cornu ammonis* subfield 1; CA3, *cornu ammonis* subfield 3; DG, dentate gyrus; SUB, subiculum.

briefly mention the main theories and their germane points, reserving further elaboration for the relevant sections below.

O'Keefe & Dostrovsky (1971) discovered that cells in the hippocampus encode the location of a rat in its environment. Each place cell fires when the rat enters the cell's preferred area (its place field) irrespective of where the rat is looking. These findings were formalized into the cognitive map theory (O'Keefe & Nadel 1978), which proposes that the hippocampus in rats and other mammals, including humans, provides a world-centered or allocentric spatial framework, as opposed to a framework where space is egocentric and represented relative to the observer him/herself. Allocentric spatial representations facilitate flexible navigation strategies as well as potentially provide a spatial scaffold upon which episodic/autobiographical memories can be built.

Allocentric space: a world-centered spatial framework of the environment

Egocentric space: space is represented relative to the observer him/herself

An alternative view of the relationship between spatial and episodic memory is offered by the relational theory, which argues that the primary function of the hippocampus is not spatial but should instead be thought of as the representation of associations between disparate elements (Cohen & Eichenbaum 1993, Eichenbaum 2004). Specifically, this theory posits the existence

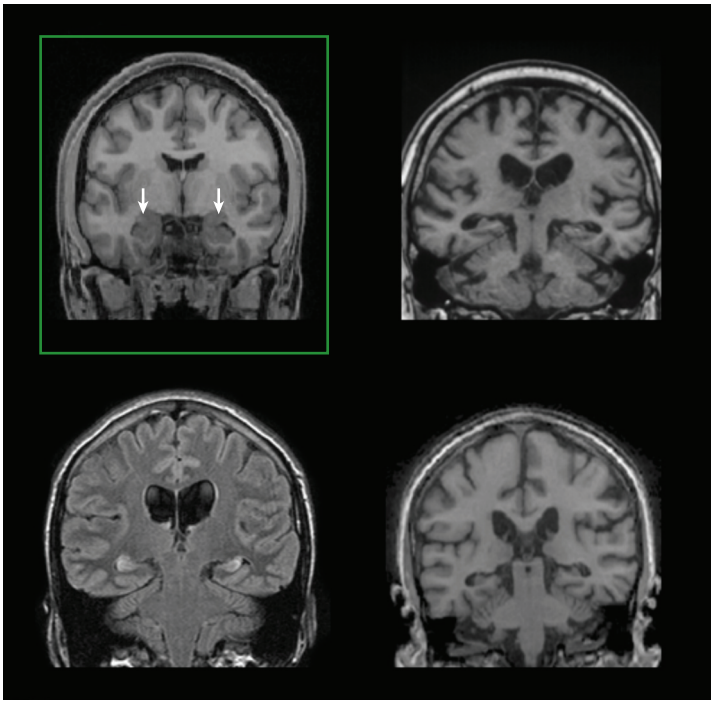

Figure 2

Examples of bilateral hippocampal damage in three patients. Within the upper left green box is a coronal section from a healthy brain, with the two hippocampi indicated by white arrows. The three other images show coronal sections from patients with damage to the two hippocampi.

of three elemental cognitive processes that are all mediated by the hippocampus—associative representation, sequential organization, and relational networking. According to this view, these fundamental properties can fully account for the spatial processing found within the hippocampus and are flexible enough to explain possible nonspatial hippocampal processes. Relational theory has parallels with other models, including the constructive episodic simulation hypothesis (Schacter & Addis 2007, Schacter et al. 2012), which suggests that the hippocampus and connected brain regions flexibly recombine elements of existing episodic memories to create new (e.g., future) scenarios, and another theory that emphasizes the hippocampal role in binding objects and contexts (Ranganath 2010).

By contrast, Hassabis & Maguire (2007, 2009; see also Maguire & Mullally 2013) have proposed that a primary function of the hippocampus is to support a process called scene construction. This is defined as the process of mentally generating and maintaining a complex and coherent scene. A scene is a spatially coherent representation of the world, small or large scale, within which an individual can potentially operate, for example, a scene of your local park or of your desktop. Scene construction necessitates the retrieval and integration of the relevant components of the scene from modality-specific cortex, which are then bound into a spatially coherent scene representation. Notably, this concept is flexible enough to account for both newly imagined scenes and retrieved episodic memories, as this core process is held to be involved in both. The authors argue that scene construction may also be critical for other functions, such as spatial navigation and planning for the future. Scene construction theory and the constructive episodic simulation hypothesis (Schacter

Scene:
a spatially coherent representation of the world, small or large scale, within which we can potentially operate

& Addis 2007, Schacter et al. 2012) are consistent with a large body of evidence suggesting that episodic memory is not simply a perfect record of past events, but instead should be considered more of a reconstructive process (Bartlett 1932, Conway & Pleydell-Pearce 2000, Schacter et al. 1998). Scene construction theory differs from the cognitive map theory in placing the creation and representation of scenes at the center of hippocampal processing, although space is important to both views.

As well as theoretical positions focusing on the nature of the information being processed by the hippocampus, some theories have considered the timescale of hippocampal involvement in memory. There is general agreement that episodic/autobiographical memories depend on the hippocampus during initial encoding (Scoville & Milner 1957). However, the role of the hippocampus in supporting such memories when they are more remote is contentious. The standard model of consolidation argues that memories (semantic and autobiographical) become less dependent on the hippocampus, eventually eschewing the need for its involvement altogether during retrieval (Marr 1971, Squire 1992, Squire & Wixted 2011, Teyler & DiScenna 1985). Alternative theories, in particular the multiple trace theory (and also the scene construction theory), propose instead that the hippocampus is necessary for retrieving vivid, contextually rich, and detailed autobiographical memories in perpetuity (Nadel & Moscovitch 1997, Winocur & Moscovitch 2011), whereas semantic information is consolidated over time such that hippocampal involvement is no longer necessary for retrieval.

The array of views outlined above demonstrates that, although a great deal is known about the hippocampus, there is still not wide agreement on the information it represents, the processes it performs, and the timescale of its involvement. By collating here instances of preserved function in the context of hippocampal damage, we hope to contribute to a more fully rounded view of the hippocampus, but also to examine whether consideration of preservation can help to reconcile, or adjudicate between, these theoretical views of hippocampal function.

NAVIGATION

Animal work points to a key role for the hippocampus in allocentric spatial navigation (O'Keefe & Dostrovsky 1971, O'Keefe & Nadel 1978). Studies in humans also support the idea of a spatial function for the hippocampus. For instance, increased gray matter volume in the posterior hippocampus is observed in individuals who have to learn very large and complex spatial layouts (Maguire et al. 2000, Woollett & Maguire 2011). During fMRI scanning, the hippocampus is engaged when subjects are mentally or virtually navigating (Spiers & Maguire 2006), and intracranial recording from electrodes implanted in the hippocampi of patients being considered for epilepsy surgery show navigation-related responses (Ekstrom et al. 2003).

Neuropsychological studies also appear to confirm the necessity of the hippocampus for spatial memory and navigation. Patients with MTL lesions have difficulty learning visual (Milner 1965), tactile (Corkin 1965), and in situ (Astur et al. 2002) mazes. The latter has also been found following focal hippocampi damage (Goodrich-Hunsaker et al. 2010). As in the rat literature, the spatial impairments are typically interpreted as being allocentric in nature (Holdstock et al. 2000).

Although patient studies have also confirmed that hippocampal damage prevents the spatial learning of new environments (Maguire et al. 2006, Rosenbaum et al. 2000, Teng & Squire 1999), evidence suggests the hippocampus is not essential for the recall of remotely learned spatial memories. Patient EP (who had extensive damage to his medial and anterior temporal lobes), although unable to learn new environments, had preserved ability to navigate in an environment he had learned many years prior to his illness (Teng & Squire 1999). He was able to describe routes between his home and local places, between different local locations, and between locations

when some streets were blocked, and he was able to determine the direction (by pointing) to particular landmarks when in a specific location. Another patient, KC (who also had widespread brain damage including the hippocampi), demonstrated a similar pattern of results (Rosenbaum et al. 2000). These two cases speak against the idea of the hippocampus being necessary for allocentric spatial tasks (as proposed by the cognitive mapping theory) and, moreover, imply that remote spatial memories are not hippocampal dependent (discordant with the multiple trace and scene construction theories).

However, it has been argued that the environments that EP and KC recalled with such accuracy had highly regular, predictable, grid-pattern layouts that may have been overlearned and therefore did not require true allocentric spatial processing (Spiers & Maguire 2007). Interesting in itself is the fact that some spatial layouts could lend themselves, over time and with extensive experience, to becoming more akin to semantic information and so not require the hippocampus for retrieval. The data from EP and KC therefore highlight that, just as with memory in general, spatial memory may also fractionate along hippocampal-dependent (allocentric) and non-hippocampal-dependent (semantic) lines. But what aspect of navigation is actually impaired in the context of focal hippocampal damage, and is it correct to let the cognitive mapping theory off the hook, so to speak, by interpreting EP and KC's preservation as akin to preserved semantic knowledge?

Another patient has extended our understanding further. TT was a licensed London taxi driver of long standing who suffered primary damage to his hippocampi (Maguire et al. 2006). TT, as with other patients with hippocampal damage, could not learn new environments. But how accurate was his knowledge of and navigation in London, a city noted for its chaotic, unpredictable, and complex layout? Compared to matched London taxi driver controls, TT could recognize and describe in detail London landmarks, and he had accurate representations of their spatial relationships and the absolute distances between them. Furthermore, he could place landmarks on a map of London and could point to the location of landmarks with high accuracy. TT could also navigate through (virtual reality) London using main artery or "A" roads. Thus, with more focal hippocampal damage and a more complex environment than EP and KC, patient TT also showed remarkably preserved allocentric spatial ability. It is therefore incorrect to say, as is often the case in the literature, that the hippocampus is essential for navigation in its entirety. These three cases show that characterizing hippocampal function in terms of allocentricity alone may not be adequate. Moreover, these findings also suggest that representations of basic relationships between landmarks, and binding or combining of information, can occur without the hippocampus at least for material learned prior to the lesions being sustained (Eichenbaum & Cohen 2014, Konkel & Cohen 2009).

Interestingly, TT became lost when navigation depended on the complex network of London's smaller roads (Maguire et al. 2006). This is unlikely to be explained by a lack of detailed knowledge of London, which TT undoubtedly possessed. Instead, TT may not have been able to visualize in advance where he needed to turn off the A roads onto the smaller roads. Indeed, TT was also significantly impaired at imagining scenes (Hassabis et al. 2007b). The data from TT also show that the hippocampus remains necessary for spatial navigation even in environments learned long ago, but in a specific way that might involve visualizing scenes of key points in the environment.

AUTOBIOGRAPHICAL MEMORY, SEMANTIC MEMORY, AND TIME

Although navigation is a function shared across species, research into the human hippocampi has also focused on memory processes that are not easily accessible in nonhumans. In particular, investigators have examined episodic or autobiographical memory, which concerns memories of our personal past experiences, and semantic memory, which refers to general knowledge (see Tulving 1972, 2002). Patients with focal bilateral hippocampal damage are consistently reported to

be unable to form lasting memories of new autobiographical events, and this is widely accepted by all theoretical models of hippocampal function. There is less agreement about whether patients can acquire new semantic information (Mishkin et al. 1998, Squire & Zola 1998, Tulving & Markowitsch 1998). Impairments in both recall and recognition for news events, famous faces, and whether famous individuals were living or dead have been found in patients with selective hippocampal damage (e.g., Reed & Squire 1998). By contrast, patient YR could recognize famous people and events that came to prominence after her hippocampal damage and could categorize famous people regarding the nature of their fame. She was impaired, however, at categorizing events and dating names and events (Holdstock et al. 2002). The status of semantic learning post hippocampal lesion is therefore not clear.

By contrast, semantic memory for information learned prelesion is preserved (e.g., Andelman et al. 2010, Lee et al. 2005b, Winocur & Moscovitch 2011), and again most theoretical positions accept that semantic information can be retrieved without the hippocampus. However, the question of whether the hippocampus is required for recalling remote autobiographical memories is hotly debated. Two patterns emerge from the literature. Some patients suffer complete loss of autobiographical memories across all time points—recent and remote (e.g., Cipolotti et al. 2001, Maguire et al. 2006, Viskontas et al. 2000). Others experience a temporal gradient, typically with recent memories lost and then preserved autobiographical memories that are more remote (e.g., Squire & Zola 1998). How remote the memories need to be before they are preserved is not clearcut, with some patients reported to have intact autobiographical memories stretching back decades (Bayley et al. 2003, Kapur & Brooks 1999, Kirwan et al. 2008). In reviewing the neuropsychological literature, Winocur & Moscovitch (2011) estimate that there is equal support across cases reported in the literature for hippocampal damage to be associated with complete loss of autobiographical memories on the one hand and preservation of more remote memories on the other.

Several possible reasons for these differing patterns have been proposed. For example, it is likely that many of our autobiographical memories become less detailed and more like semantic memories over time (so-called semanticization). This could explain the apparent preservation of remote autobiographical memory in some patients (Winocur & Moscovitch 2011). It could also be the case that those patients with more extensive loss of remote autobiographical memories had more widespread and covert damage (e.g., Reed & Squire 1998). However, neither of these explanations is adequate to account for the contrary evidence. Autobiographical memory and consolidation are of central importance to memory neuroscience because they speak fundamentally to the type of information the hippocampus represents and, by inference, the timescale of its involvement and the processes involved. Yet elucidation of the neuropsychology seems deadlocked.

The fMRI studies of healthy participants have more often supported the view that the hippocampus is necessary for retrieving vivid autobiographical memories in perpetuity (Gilboa et al. 2004, Maguire et al. 2001, Maguire & Frith 2003, Ryan et al. 2001). Of course, fMRI shows brain areas that are involved in, but not whether they are necessary for, a task. Recently, Bonnici et al. (2012) used a different type of method to analyze fMRI data acquired during autobiographical memory recall. Multivoxel pattern analysis (MVPA) can be used to establish whether information about a memory is represented in the pattern of fMRI activity across voxels in the hippocampus (Chadwick et al. 2012). Bonnici et al. (2012) found that information about both recent (two-week-old) and remote (ten-year-old) autobiographical memories (matched across factors such as vividness and detail) was represented in the anterior hippocampus (MVPA classification accuracies were significantly above chance for the two types of memories and were not significantly different from each other). On the other hand, in the posterior hippocampus (and ventromedial

prefrontal cortex), classification accuracies were significantly higher for remote memories than recent memories. Further examination revealed that the posterior hippocampal findings were specific to subregion CA3 and the dentate gyrus (Bonnici et al. 2013).

These results suggest that some kind of change has indeed taken place between recent and remote autobiographical memories, and this is reflected not only in a change in hippocampal-cortical involvement, but also within the hippocampus itself—which is not predicted by any theory. The anterior hippocampus may perform a function that is common to both recent and remote memories (perhaps scene construction; Zeidman et al. 2014), whereas remote memories require more of whatever process is going on in the posterior hippocampus—perhaps the reinstatement of the spatial context (Woollett & Maguire 2011). More generally, these data indicate that the mixed pattern of preserved or impaired remote autobiographical memory observed within the neuropsychological literature may depend on the location and extent of the damage within the hippocampus itself.

The precise role of the hippocampus in autobiographical memory is crucial to resolve, and going forward we believe that using fMRI with patients with hippocampal damage could reveal information about the functionality of remaining hippocampal tissue and its location, as can techniques such as MVPA. What are urgently needed are longitudinal fMRI studies that follow autobiographical memory representations over long time periods (i.e., years) to examine if and how memory traces change over time and concomitant neural responses. These are very challenging fMRI studies to conduct, however, and there are none that we are aware of in the literature to date.

Implicit in autobiographical memory is the notion of time—memories can be recent or from far back in time, and we can also project ourselves forward in time (so-called mental time travel) (Tulving 1972, 2002). Neurons that appear to respond to time have been found in the rodent hippocampus (MacDonald et al. 2011), although an fMRI study in humans found that frontal and parietal cortices, but not the hippocampus, supported mental time travel (Nyberg et al. 2010). Time, however, can be construed in different ways, and an in-depth discussion of time is beyond the scope of this article (for reviews, see Eichenbaum 2014, Hassabis & Maguire 2007). However, it is interesting to consider some instances of preserved time-related processing.

We know, for example, that patients with bilateral hippocampal damage can do basic tasks, such as arrange pictures into a sequence to make a logical story, and are able to recombine elements in narratives to ensure that a logical story unfolds (Mullally & Maguire 2014). Although patients have lost the ability to recall their past (and imagine the future; see Imagination section), they still understand the concept of time (Craver et al. 2014b). For example, patient KC, who has widespread damage that includes the hippocampi bilaterally, performed comparably to control participants in being willing to trade a smaller, sooner reward for a larger, delayed reward (temporal discounting; Kwan et al. 2012). If his concept of time was impaired, we would expect him to always choose the reward in the present regardless of the value of a future reward. Furthermore, KC made decisions that would affect future rewards in the same way as control participants made decisions, demonstrating that although he could not imagine future experiences, he could, on some level, still travel in time (Craver et al. 2014a).

EMOTION AND THEORY OF MIND

Even though patients with bilateral hippocampal damage cannot form new autobiographical memories, they can still be affected emotionally by events over time. Although fear (Bechara et al. 1995) and eyeblink (Gabrieli et al. 1995) conditioning were unaffected following bilateral hippocampal lesions, explicit memory for the conditioning was lost. Additionally, after viewing emotional film

clips (either happy or sad), patients' mood remained inducted even though they could not remember details of the film (Feinstein et al. 2010). Further, patients could produce as many emotional memories from before their lesion (the majority of which were positive) as could controls, and when memories were rated on emotional intensity by independent raters, ratings were equal to those of controls (Buchanan et al. 2005). On the other hand, when rated for emotional intensity by the patients themselves, memories were rated as less intense.

Yet, although patients with hippocampal damage seem to have retained emotional responses (i.e., the emotion generated when an event is happening), their anxiety response is impaired. For example, in response to a standardized stress test (public speaking), patients showed increased heart rate and affective responses, as did control participants, but no cortisol response—cortisol has been associated with anxiety (Buchanan et al. 2009). Additionally, in a virtual foraging environment, patients were not affected by changes in threat level, and they spent less time in the "safe place" and behaved less cautiously over time compared to controls despite explicit knowledge of the threat level (Bach et al. 2014). Thus, patients show reduced approach-avoidance behavior when there is a potential threat (i.e., anxiety, not fear). This differentiation in patients accords with findings described in the animal literature, suggesting a distinction between the brain circuitry involved in fear, which is thought to be processed by the amygdala, and anxiety, which is thought to be mediated by the hippocampus (Gray & McNaughton 2003, McHugh et al. 2004). Another study suggests that even though patients with hippocampal damage can experience emotions, their empathy—the ability to share and understand the feelings of others—is reduced. Questionnaire measures (completed by patients and family members) suggested lower trait empathy, and patients were unaffected by empathy inductions via auditory recording and written notes (Beadle et al. 2013).

Empathy: the ability to share and understand the feelings of others

Theory of mind: the ability to infer the mental states of others

The ability to empathize would seem to be related to theory of mind, which allows an individual to infer the mental states of others. Theory of mind has been reported as intact following hippocampal damage. Patient KC (and a second similar patient, ML), who had widespread damage that included the hippocampi bilaterally, performed at the same level as controls on a range of theory-of-mind tasks (Rosenbaum et al. 2007). This finding is interesting to consider in the light of the report of reduced empathy following hippocampal lesions (Beadle et al. 2013). Being able to logically understand what someone else knows, including their emotional state (as in theory of mind), may be different from fully experiencing someone else's emotional state (as in empathy). Support for this difference comes from a study examining counterfactual (CF) thinking, where patients with focal bilateral hippocampal pathology showed intact high-level causal inference, which allowed them to logically infer the thoughts and emotional state of a protagonist in an emotional event without needing to simulate or experience the event or emotions (Mullally & Maguire 2014). In a way, this distinction could be considered similar to that between semantic and episodic memory. It is also interesting to note that when healthy participants were presented with a situation depicting another individual in difficulty, imagining themselves helping the person (episodic simulation) or recalling an event from their past where they helped another (episodic memory) led to increased prosocial intentions (Gaesser & Schacter 2014). That is, engaging elements of episodic processing to help fully experience the event rather than just observing it boosted participants' empathy, thus suggesting a link between episodic memory and empathy.

Overall, therefore, basic emotional processing and the ability to feel emotions "in the moment" as well as to logically infer in factual terms the thoughts and feelings of others appear to be preserved in patients with bilateral hippocampal damage. What these patients cannot seem to do is imagine another person's situation in order to fully experience that person's emotions, which may not be a deficit in emotion per se, but rather an impairment of constructing another's situation.

RECOGNITION MEMORY

Recollection: the retrieval of contextual details associated with a previously experienced event

The recall or reexperiencing of autobiographical memories is often contrasted with recognition memory, which is the ability to recognize previously encountered events, objects, or people. It is typically subdivided into two component processes: recollection and familiarity, often referred to as remembering and knowing, respectively. Recollection is the retrieval of contextual details associated with the previously experienced event. By contrast, familiarity is the feeling that the event was previously experienced, but without recollection of the associated details or context (for reviews, see Gardiner & Parkin 1990, Tulving & Thomson 1973, Yonelinas 2002).

The role of the hippocampus in recognition memory is hotly debated. Some researchers suggest that all recognition memory (with the exception of faces; see below) requires the hippocampus (e.g., Smith et al. 2014a). Others believe that recollection is dependent on the hippocampus, but familiarity is not (Brown & Aggleton 2001, Eichenbaum et al. 2007). Another view is that hippocampal involvement is stimulus dependent, being required for recognition of across-domain pairs of items (e.g., a picture and a sound) but not single items or within-domain (e.g., picture-picture) pairs (e.g., Mayes et al. 2007).

This is an entrenched debate, and as with autobiographical memory, there is neuropsychological evidence from patients with focal hippocampal damage to support each perspective. We cannot do justice to this substantial literature in our limited space here, and others have written eloquently and at length about it elsewhere (Brown & Aggleton 2001, Eichenbaum et al. 2007, Yonelinas 2002). Therefore we limit ourselves to making just a few observations.

One consistent result is that of preserved face recognition (Aggleton & Shaw 1996, Bird & Burgess 2008, Mayes et al. 2004, Smith et al. 2014a), although this may only be at short delays (Smith et al. 2014a). In an exceptionally thorough examination of recognition memory across different types of stimuli (including words, faces, buildings, and objects), patient YR's forced choice, Yes/No, and intra-item associations, as well as associations between items of the same category, were preserved (Mayes et al. 2004). YR was impaired only on recognition tests for associations between items of different kinds (e.g., words and faces), a finding that has been replicated (e.g., Holdstock et al. 2005, Konkel et al. 2008).

The consistent finding of preserved face recognition may seem at odds with YR's impaired recognition of associations across domains. However, a face—in contrast to other complex stimuli—is thought to be processed as a whole entity and not as multiple component parts (e.g., Tsao & Livingstone 2008). An interesting contrast to faces is that of scenes. Scene stimuli are complex stimuli in that they are made up of multiple features. Unlike faces, however, scenes are thought to be processed by combining each individual feature. Notably, despite preserved ability to recognize faces, patients with focal hippocampal damage are typically impaired at recognizing scenes (Taylor et al. 2007).

Thus, preserved recognition memory following hippocampal damage may occur for two reasons: first, if a familiarity process can be used and not a recollective one (Eichenbaum et al. 2007); second, provided the internal representation of a spatially coherent scene/context is not required (Lee et al. 2012, Maguire & Mullally 2013, Zeidman et al. 2014).

WORKING MEMORY

When performing a number of the above tasks, working memory may be engaged. Working memory is the transient holding online of information; for example, maintaining stimuli in mind to decide upon whether they are old or new at short delays. Working memory has traditionally been regarded as immune from hippocampal damage. Indeed, standard tests of working memory (e.g.,

digit span) are preserved following such damage (e.g., Andelman et al. 2010, Goodrich-Hunsaker & Hopkins 2009, Hopkins et al. 2004, Victor & Agamanolis 1990, Warren et al. 2012).

Experimental tests of working memory also indicate preservation. The eye movements of patients with hippocampal damage had patterns similar to those of control participants when shown a manipulated scene soon after the original, a finding that suggests spared working memory (Ryan et al. 2000, Ryan & Cohen 2004). Further, during the spatial exploration of masked scenes (the scene could be seen only through a moveable window), patients with hippocampal damage were able to successfully relocate to their original start location from the goal object within each trial (Yee et al. 2014). Additionally, working memory in patients has been shown to be preserved for single objects or single locations (Olson et al. 2006a,b).

However, other investigations suggest that working memory might not be completely hippocampal independent (e.g., Ranganath & Blumenfeld 2005, Yonelinas 2013). Although working memory is preserved for single items, more complex associations that require combining elements together led to impaired working memory, for object-location (Olson et al. 2006a,b), face-scene, and object-scene (Hannula et al. 2006, 2015) relations as well as for topographical stimuli (Hartley et al. 2007). Moreover, magnetoencephalography work suggests increased hippocampal theta synchronicity with occipital and temporal regions during working memory maintenance of scenes (Cashdollar et al. 2009).

Thus, working memory seems to be preserved following hippocampal damage for single items and locations. However, impairments are reported when more complex stimuli, typically involving scenes, are used.

VERBAL MEMORY

Although debates rage about hippocampal contributions to some of the memory types outlined above, one form of memory is invariably compromised by bilateral hippocampal lesions: verbal memory. Patients cannot recall lists of single words (Buchanan et al. 2005), word-pair associates (Cipolotti et al. 2006), and verbal narratives (Barense et al. 2007). Why might this be the case, given that single words do not require any associative binding, and none of this verbal material appears to involve allocentric processing, object-context binding, or the internal construction of scenes?

Standardized verbal memory tests (e.g., the Warrington Word Recognition Memory Test, the Wechsler Memory Scale word-pair associates and logical memory subtests, and the Rey Auditory Verbal Learning Test) all use concrete words that represent specific imaginable items (Paivio 1969). One speculation offered by Maguire & Mullally (2013) is that people may automatically use imagery, such as scenes, during encoding and retrieval of concrete verbal material. For instance, we might visualize the scene within which a story is unfolding, or we might place the items described in word pairs in a simple scene together. Despite the rise and fall of imagery-based memory theories across the decades (Paivio 1969), evidence suggests that visual imagery not only boosts pair-associate recall in healthy participants but also enables patients with left temporal lobectomies to partially compensate for their verbal memory deficits (Jones 1974). If verbal memory tasks routinely benefit from the use of imagery-based mnemonic strategies, and if hippocampal amnesic patients have difficulty imagining scenes (Hassabis et al. 2007b), they would be disadvantaged on such tasks. This, then, gives rise to the clear prediction that the patients should be less impaired when learning and recalling abstract words.

Abstract words typically represent ideas and concepts and, as such, they are much less imageable. From the literature, it is surprisingly difficult to ascertain whether memory for abstract words is preserved following focal bilateral hippocampal damage, as most tests and studies have used

concrete, imageable words. In contrast, in patients who had unilateral temporal lobectomies for the relief of intractable epilepsy, abstract words have been examined. Patients with right temporal lobectomy were found to have impaired memory for concrete word pairs but preserved memory for abstract word pairs in comparison with controls (Jones-Gotman & Milner 1978; see also Jones-Gotman 1979). Moreover, whereas greater hippocampal lesion extent was associated with a bigger drop in performance on concrete word pairs, lesion size had no effect on abstract word-pair performance.

Further work suggests that imageability may be key to understanding this pattern of preservation and impairment (Jones-Gotman 1979). Patients and control participants were presented with a list of mixed concrete and abstract words. They were asked to visualize some words and to pronounce others; after a delay, they had to recall the word list. Patients with right temporal lobectomy performed comparably to control participants for both concrete and abstract words when the words were previously pronounced, but their performance was inferior on both abstract and concrete words when the words were previously visualized. A greater extent of hippocampal lesion was associated with impaired performance on visualized concrete words but had no relationship with the other conditions. Imageability of words therefore seems to be important to understanding the relationship between words and the hippocampus. In further support of this theory, Gold et al. (2006) and Kirwan et al. (2010) found that patients with bilateral hippocampal damage were impaired at both word recognition and recall with mixed concrete and abstract words. However, for the abstract words these investigators explicitly required the patients to learn by imagining an indoor or outdoor scene, which likely explains their impairment, given that patients with hippocampal damage are unable to imagine scenes (Andelman et al. 2010, Hassabis et al. 2007b, Mullally et al. 2012a, Race et al. 2011, Rosenbaum et al. 2009).

It could be that abstract words simply require greater effort and memory search to develop a representational image (Kieras 1978) but thereafter are processed like concrete words. If this is the case, then a significant overlap should exist in the brain networks supporting the processing of concrete and abstract words in neuroimaging studies of healthy participants. However, extant data show differences in the brain networks for processing abstract and concrete words (e.g., Binder et al. 2005, Wang et al. 2013).

The majority of hippocampal theories have a visuospatial bias (Bird et al. 2012, Maguire & Mullally 2013, Moscovitch et al. 2006, O'Keefe & Nadel 1978, Ranganath 2010, Schacter & Addis 2009). Accounting for verbal memory deficits is therefore challenging. If, however, there is a distinction between abstract and concrete memoranda, and processing of the former is preserved following bilateral hippocampal lesions, this would have important implications for understanding and conceptualizing hippocampal processing. It is therefore surprising that abstract verbal material has featured so little across the decades of research involving patients with bilateral hippocampal damage. This gap in our knowledge clearly needs to be addressed.

LEARNING

As observed previously, the acquisition of new episodic information, such as autobiographical events, is compromised in the context of bilateral hippocampal damage, whereas reports are mixed concerning the preservation of semantic learning. Patients who sustained their bilateral hippocampal damage very early in life display instances of preserved learning and other interesting features (see sidebar Developmental Amnesia). However, our main focus here is in asking whether patients whose bilateral hippocampal damage occurred in adulthood can learn and retain any kind of new information. There is an extensive literature on preserved priming and implicit learning in amnesia that we cannot cover here, and so we refer the reader to a recent review (Reber

DEVELOPMENTAL AMNESIA

Developmental amnesia (DA) occurs following a hypoxic/ischemic incident perinatally or in early childhood that results in bilateral hippocampal pathology (Gadian et al. 2000; Vargha-Khadem et al. 1997, 2003). A distinguishing feature of DA compared to hippocampal damage sustained in adulthood is that the content of semantic memory and world knowledge, which is rich and age appropriate, has been learned after the onset of hippocampal pathology. This contrasts with the autobiographical memory of those with DA, which is impaired. This memory pattern may indicate that semantic learning is hippocampal independent, although reorganization of the developing brain in the presence of hippocampal damage could be a contributing factor. Also in contrast to adult patients (e.g., Hassabis et al. 2007b), individuals with DA appear to have preserved ability to imagine fictitious and future scenes (Cooper et al. 2011, Hurley et al. 2011, Maguire et al. 2010b). However, this seems to rely on their intact semantic and world knowledge—individuals with DA describe it as an effortful process and one where they are unable to actually visualize the scenes in their mind's eye. Moreover, unlike control participants, the remnant hippocampal tissue in well-characterized DA patient Jon was not significantly activated while he constructed scenes during fMRI (Mullally et al. 2014).

2013). We limit this section to reflections on other aspects of preserved learning that have not received such extensive coverage.

Patient HM displayed some implicit learning; for example, his motor skills improved on a tapping task and two tracking tasks (where a drum rotated and he was required to keep contact with a specified track with just one hand or with both hands simultaneously), even though he had no memory of previously performing the tasks (Corkin 1968). Implicit learning has also been shown for digit, spatial location, word, and pseudo-word sequences (e.g., Gagnon et al. 2004) and for procedural learning, including geometric figure tracing, weaving, and pouring liquid into multiple containers from a height (Cavaco et al. 2004). Long-lasting priming (up to seven days) involving verbal material (e.g., word stem completion and word pairs) and object naming has also been reported in patients (Schacter et al. 1993, Tulving & Schacter 1990). By contrast, mixed results have been reported for visuospatial search, in which participants had to locate a rotated "T" within a display of rotated "L" distractors. Results originally suggested that patients showed no priming (Chun & Phelps 1999), but a later study suggested otherwise (Manns & Squire 2001). Thus, priming over a more complex scene display may be reduced in comparison with priming for single items.

Some elements of probabilistic learning are also preserved in patients with bilateral hippocampal damage. This preservation concerns tasks in which the associations between stimuli and responses are probabilistic; thus, information from a single trial is not reliable, nor is it as relevant as information accrued across many trials. During initial learning trials, learning rates have been reported as equal between patients and controls (Knowlton et al. 1996, Reber et al. 1996). However, after continuous training (e.g., more than 50 learning trials), controls began to outperform patients (Knowlton et al. 1994), possibly because controls begin to use more complex strategies to learn outcomes (Meeter et al. 2006). However, although initial learning could take place, when outcome probabilities were changed, patients did not change their responses, suggesting an impairment in flexibly using the acquired knowledge (Shohamy et al. 2008).

By contrast, another study found that probabilistic learning in patients was impaired across the board (Hopkins et al. 2004). In this study, while patients' scores remained at approximately the same level as previously reported, control participants' scores increased to much higher levels. Further, when a similar paradigm—but deterministic learning and configural (i.e., combined)

elements—was used, patients were impaired compared to control participants (Kumaran et al. 2007). Two patients in this latter study showed better learning than the other patients, suggesting that they had some ability to combine information; however, on debriefing the patients indicated that although they had formed associations between outcomes and individual combined patterns, they could not relate the patterns to each other. Thus, it seems that even when some basic elements of associative learning are retained, the ability to integrate and use this information may be lost in the context of hippocampal damage.

Fast mapping: the process by which children rapidly acquire new words, whereby new associations are discovered and not deliberately learned

Another type of learning, collaborative learning or learning within a common ground, has been found to be intact following bilateral hippocampal lesions (Duff et al. 2006). Over time, patients needed to use fewer words to generate labels for abstract objects when describing them to a known partner. Further, this label knowledge was retained at six months. However, the patients could not remember the objects themselves—although the shortened labels created in common ground were retained, the objects needed to be present for the patients to describe them (Rubin et al. 2011).

In another examination of associative learning, patients with damage to the hippocampus and wider MTL learned (and retained at one week) arbitrary associations via fast mapping despite impairment on a matched standard association task (Merhav et al. 2014, Sharon et al. 2011). Fast mapping is the process by which children rapidly acquire new words (Carey & Bartlett 1978) and involves actively discovering associations instead of deliberate learning. However, two other studies failed to find preserved learning following fast mapping (Smith et al. 2014b, Warren & Duff 2014). The reasons for this disparity are not clear, and more work on fast mapping is required to better understand the parameters within which such learning might be possible.

In summary, patients with bilateral hippocampal damage are able to form arbitrary associations, particularly when learning is implicit. Yet patients typically do not remember how or where the information was obtained, nor can they flexibly use the acquired information. The knowledge therefore seems to lack a backdrop or a context, and a time or place—a theme that runs through several hippocampal theories (Buzsaki & Moser 2013, Eichenbaum & Cohen 2014, Maguire & Mullally 2013).

VISUAL PERCEPTION

The hippocampus receives a large number of inputs from multiple sensory modalities and in particular from vision (Felleman & Van Essen 1991). It may be that preserved or impaired cognitive functions could in fact arise from a basic processing level, namely that of visual perception. Traditionally, visual perception has been reported as preserved following hippocampal damage (Scoville & Milner 1957; see also Lee et al. 2005b, Spiers et al. 2001). Moreover, a series of studies suggests that focal bilateral hippocampal damage predominantly leaves visual discrimination abilities intact for material such as faces, single objects, abstract art, and colors. There is one exception: Patients could not discriminate between scenes (Graham et al. 2006; Lee et al. 2005a,b).

Hippocampal engagement during the perception and discrimination of scenes has been shown in fMRI studies of healthy participants (Barense et al. 2010, Lee et al. 2008, Mundy et al. 2012). Zeidman et al. (2014) recently investigated the hippocampal response to visually perceiving scenes, constructing scenes in the imagination, and maintaining scenes in working memory. They found extensive hippocampal activation for perceiving scenes and a circumscribed area of anterior medial hippocampus common to scene perception and scene construction (**Figure 3**). Hippocampal activity was significantly lower for maintaining scenes in working memory. Further evidence from patients and from fMRI in healthy participants suggests that the hippocampus is engaged in

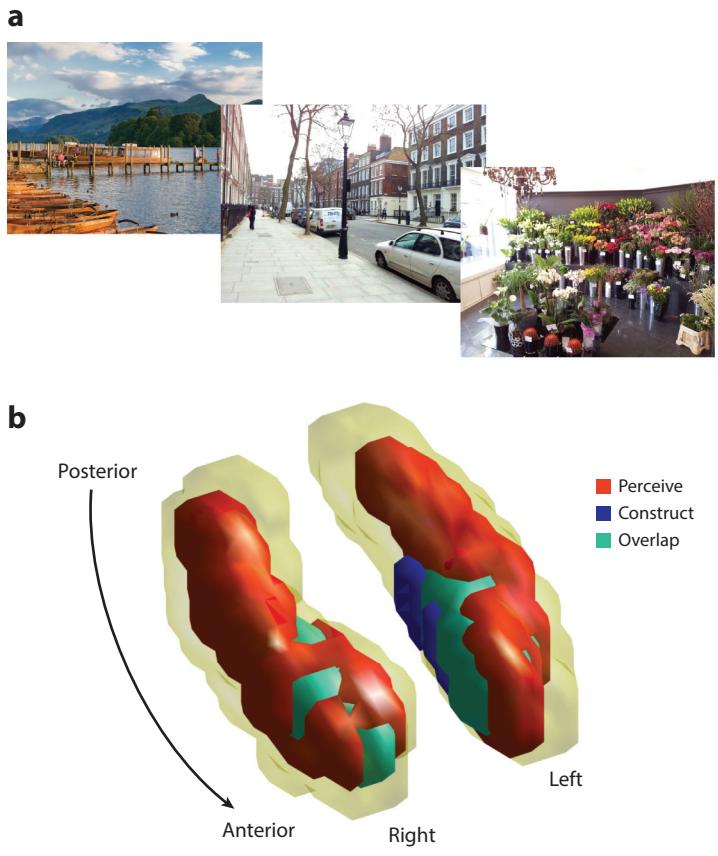

Figure 3

Scene processing and the hippocampus. (*a*) Examples of scenes used in the scene-viewing condition of Zeidman et al.'s (2014) functional magnetic resonance imaging study. (*b*) A schematic of the two hippocampi from that study indicating activity associated with viewing scenes and constructing scenes in the mind's eye, and an area in anterior medial hippocampus of maximal overlap in the activity associated with these two conditions.

perception when discriminating strength-based perception (the global entity) but not state-based perception (local visual features; Aly et al. 2013), highlighting region CA1 in particular (Elfman et al. 2014).

However, patients have also been reported to have preserved visual perception and stimulus discrimination regardless of the stimuli used (Kim et al. 2011, Shrager et al. 2006). These authors suggest that impairments in visual perception observed elsewhere are in fact due to discrimination ability not improving over time as in control participants, overloading of working memory, or long-term memory-encoding deficits (Kim et al. 2011, Knutson et al. 2012). Zeidman et al. (2014) recently described how differences across the patient scene perception literature could be reconciled. They propose that whether scene perception is preserved or impaired in patients with hippocampal lesions may depend on whether a task requires an internal model of a spatially coherent scene to be constructed. We elaborate further on this idea below.

IMAGINATION

When, in 1992, HM was asked what he believed he would do tomorrow, he replied, "Whatever is beneficial" and appeared to have "no database to consult when asked what he would do the next day, week, or in years to come" (S. Corkin, personal communication; cited in de Vito & Della Sala 2011). Similar anecdotal evidence of problems in imagining the future was reported in patient KC (Rosenbaum et al. 2005, Tulving 1985; see also patient DB in Klein et al. 2002). Hassabis et al. (2007b) formally tested a group of patients with more focal bilateral hippocampal pathology and found they were unable to imagine personal future scenarios and fictitious scenes. They reported that their attempted scenes were spatially fragmented. Providing the scene elements to the patients did not improve their performance. Subsequently, this scene construction deficit was replicated across different laboratories and in different sets of patients with hippocampal damage (Andelman et al. 2010, Mullally et al. 2012b, Race et al. 2011, Rosenbaum et al. 2009), with the exception of one study in which scene construction ability was reported to be preserved (Squire et al. 2010). It is notable that the patients in this latter study did not exhibit pervasive autobiographical memory loss (see also Kirwan et al. 2008). As such, this finding in fact provides further support for the scene construction theory, which posits that if patients have intact autobiographical memory, then they should also have preserved scene construction ability, because the former depends on the latter (Maguire & Mullally 2013; see also Maguire & Hassabis 2011 and Mullally et al. 2012a). Hippocampal engagement during scene construction/simulation tasks has been confirmed in fMRI studies of healthy participants (Addis et al. 2007, Hassabis et al. 2007a). Interestingly, Hassabis et al. (2007b) found that one patient with bilateral hippocampal damage could construct scenes, and during fMRI this was associated with significant activation of the remnant tissue of his right hippocampus (Mullally et al. 2012a).

Although the inability to imagine fictitious or future scenes is striking, it is equally informative to consider related preservations. Patients with hippocampal damage were able to imagine single isolated objects and could list relevant associated items; they simply could not visualize them in a coherent scene (Hassabis et al. 2007b, Mullally et al. 2012a). Patients tested by Mullally et al. (2012b) and Race et al. (2013) could richly describe pictures of scenes that were put in front of them, which in the latter study included forming detailed narrative descriptions of scene images, suggesting that basic scene perception was intact. This seems at odds with the findings of impaired scene perception described in the previous section.

Further clues about the role of the hippocampus in scene processing come from the study of boundary extension (BE) (Intraub & Richardson 1989). BE is a cognitive phenomenon whereby people erroneously remember seeing more of a scene than was present in the sensory input; it occurs because when we view a scene, we implicitly extrapolate beyond the borders to form an extended representation of that scene. In the absence of the original visual input, this extended scene is remembered instead of the original input, causing a memory error. BE is a robust and consistent effect and, of note, only occurs in relation to scenes and not single isolated objects (Gottesman & Intraub 2002), a dissociation that mirrors the imagination dichotomy observed in patients with hippocampal damage (Hassabis et al. 2007b).

Mullally et al. (2012b) found that patients with focal bilateral hippocampal damage had significantly attenuated BE. They did not extrapolate as much as controls beyond the view in scenes they were shown, and this paradoxically led to significantly better memory for the scenes compared to the control participants (for other examples of paradoxical facilitation following brain lesions, see Kapur 2011). BE depends on the ability to imagine beyond the view in a scene, and having lost this ability, the patients were then less susceptible to the BE effect. An fMRI study of healthy participants confirmed the engagement of the hippocampus during BE (Chadwick et al. 2013).

Mullally et al. (2012b) showed patients a picture of a scene and asked them to imagine what might be beyond the view. Although patients could generate as many context-appropriate details as control participants and could associate them with each other and the context, they made significantly fewer spatial references and were unable to visualize the extended scenes in their mind's eye.

Kim et al. (2015) recently tested most of the same patients who were examined by Squire et al. (2010) and have reported that these patients showed normal BE, thus disputing the idea that the hippocampus is required for scene construction. They also questioned the degree of hippocampal volume loss reported in Mullally et al.'s (2012b) patients. In fact, Kim et al. (2015) made a factual error on this latter point. They incorrectly claimed that two of Mullally et al.'s (2012b) patients had hippocampal volume loss greater than 70%. As stated by Mullally et al. (2012b), the volumes were reduced to (not by) 68.7% to 78.33% of normal, rendering redundant their arguments about this point.

Concerning their BE findings, it is not surprising that Kim et al. (2015) found normal BE in their patients, given that BE depends upon scene construction ability, which was shown to be intact in these patients (Squire et al. 2010). Moreover, Kim et al. (2015) changed critical elements in how BE was tested, which may have fostered null results (see Maguire et al. 2015). Critically, BE weakens as stimulus view widens (Hubbard et al. 2010). To enhance sensitivity to group differences, in Mullally et al. (2012b) very tight close-ups were selected for the BE drawing task (objects filled 43.4% of the space). By contrast, Kim et al. (2015) used more wide-angled photographs (objects filled 30.2% of the space), thus reducing the ability to distinguish group differences. In addition, Kim et al. (2015) more than doubled the number of trials typical for this method (Mullally et al. 2012b; see also Hubbard et al. 2010). This raises concerns, given that such trial limitations were used to minimize intertrial effects on memory. Kim et al.'s (2015) experiment 2b is especially surprising because participants were explicitly discouraged from selecting the correct ("the same") response, thus biasing the experiment away from finding attenuated BE and consequently, once again, restricting the opportunity for detecting group differences. We therefore believe that the patients tested in Squire et al. (2010) and Kim et al. (2015), who were without pervasive autobiographical memory deficits, and features of the testing in both studies may go some way toward accounting for the anomalies between their results and others in the literature.

One other apparent preservation is relevant to consider here. We often engage in counterfactual (CF) thinking, which involves reflecting on what might have been. Creating alternative versions of reality seems to have parallels with recollecting the past and imagining the future (for more on CF thinking, see Schacter et al. 2015). Given that these are impaired in patients with hippocampal damage, we might predict that CF thinking would be compromised following hippocampal damage. Testing nonpersonal CF thinking, Mullally & Maguire (2014) found that patients could deconstruct reality, add in and recombine elements, and change relations between temporal sequences of events, enabling them to determine plausible alternatives of complex episodes. However, a difference between the patients and control participants emerged in the patients' subtle avoidance of CF simulations that required the construction of an internal spatial representation. These findings suggest that mental simulation in the form of nonepisodic CF thinking does not seem to depend upon the hippocampus unless there is the added requirement for construction of a coherent spatial scene within which to play out scenarios.

In summary, it may be that healthy individuals are never passively perceiving scenes because the BE effect, underpinned by scene construction, always occurs and engages the hippocampus. Thus, without a model of a scene being constructed in the hippocampus, the scene currently in view can only be comprehended in isolation and cannot be extended beyond its borders or in one's imagination. It is for this reason Zeidman et al. (2014) proposed that scene perception tasks that require the generation of an internal model of a scene (as is typically required in scene

discrimination tasks) are dependent upon the hippocampus. Maguire & Mullally (2013) go further and suggest that any task or any aspect of cognition that requires an internal model of a scene will be adversely affected by bilateral hippocampal lesions.

THEORETICAL IMPLICATIONS AND CONCLUSIONS

Here we surveyed the literature across numerous cognitive tasks to collate instances of preserved, and even facilitated, performance in patients with focal bilateral hippocampal damage. What is striking in the first instance is the nature of the preservations. For example, we are accustomed to reading in the literature that navigation is impaired in patients with focal bilateral hippocampal damage, but this kind of sweeping statement belies the facts. In terms of environments learned prelesion, only one specific aspect of navigation seems to be impaired, whereas performance on the majority of tasks assessing even high-level allocentric spatial memory and knowledge are all intact. In other instances, a lack of empirical studies precludes a proper evaluation of hippocampal involvement. Verbal memory is a case in point, held to be a paradigmatic example of impairment following hippocampal lesions, and yet there is a dearth of studies examining patients' ability to learn abstract verbal memoranda. Given such gaps in our knowledge and accepting that theories are formulated on more than neuropsychological evidence alone, how do the theoretical accounts we outlined earlier hold up when the preservations described here are considered?

Rather than focusing on specific instances of preservation and their implications for each theory, it is perhaps more useful to ask whether any clear or unifying themes emerge from the data as a whole. By concentrating on commonalities across different aspects of memory and cognition, we can to some degree guard against the interpretational issues summarized at the outset.

We believe that the patterns of preservation noted here help isolate a core problem that patients with focal bilateral hippocampal damage face. They cannot construct a spatially coherent model of the world. In other words, they are unable to construct internal representations of scenes. They seem unable to visualize in advance when to make turnings onto smaller roads during navigation, they cannot reconstruct scenes of past events or imagine scenes in the future, they are impaired at constructing another person's situation to experience that person's emotions, and they have deficits in recognition memory and working memory, specifically for scenes. Their learning is devoid of a context, and their perception—specifically of scenes—is compromised when internal models of scenes need to be generated. They show attenuated BE, leaving them access to only what is in front of their eyes.

Considering current theories, we believe the scene construction theory can best account for the patterns of impairment and preservation across these functional domains (Hassabis & Maguire 2007, 2009; Maguire & Mullally 2013). A purely allocentric account (O'Keefe & Nadel 1978) or a purely associative/relational model (Konkel et al. 2008) are not completely satisfactory given that patients appear to retain aspects of these abilities in some shape or form. Viewing the core function of the hippocampus as constructing spatially coherent scenes helps to explain the role of the hippocampus in a diversity of cognitive functions that extend beyond memory. As noted by Maguire & Mullally (2013), the hippocampus is not solely responsible for all of these functions, but rather it contributes a key ingredient—scene construction. This is why considering preservations is vital for aiding interpretation; the many aspects of navigation and memory that are preserved following hippocampal damage make sense because they do not require the internal construction of scenes. We note that at this time the scene construction theory has not been tested directly in relation to all the preservations and deficits that follow hippocampal damage. This in particular applies to verbal memory, although the majority of hippocampal theories have a similar visuospatial bias (Bird et al. 2012, Maguire & Mullally 2013, Moscovitch et al. 2006, O'Keefe & Nadel 1978,

Ranganath 2010, Schacter & Addis 2009), and accounting for verbal memory deficits is a universal challenge. We also appreciate that others have different views and have noted that the reader may wish to take into account evidence purported to speak against the scene construction theory (e.g., Kim et al. 2015, Squire et al. 2010).

Finally, we acknowledge that we are stakeholders in the scene construction theory and that others with divergent views may come to different conclusions after reflecting on the patterns of preservation we have collated here. We welcome debates that consider all of the evidence. Overall, our hope is that people take preservations into account to a greater extent in their empirical studies and their theoretical models of the hippocampus and memory, that they begin to make principled predictions about preservations as well as deficits, and that the findings surveyed here stimulate new questions about the old issues of what the hippocampus does and how memory works.

SUMMARY POINTS

1. Neuropsychological studies are dominated by the lesion-deficit model, and preservation of function following brain damage receives less attention.
2. Considering preservation of function following focal bilateral hippocampal damage could help to inform, refine, or refute extant models of the hippocampus and memory.
3. We collated evidence across a range of functional domains concerning preservations following focal bilateral hippocampal lesions.
4. Although not exhaustive, this review revealed some unexpected abilities, new angles on extant beliefs, and surprising gaps in our knowledge.
5. Overall, when considered in their totality, the data appear to suggest that patients with hippocampal damage cannot construct spatially coherent models, or scenes, of the world, and this may explain their pattern of performance across disparate aspects of cognition.
6. We believe that the scene construction theory may be best able to account for the preservations and deficits that arise from focal bilateral hippocampal damage.

FUTURE ISSUES

1. Presentation of neuropsychological data would be improved by routine reporting of effect sizes and confidence intervals and by showing all data from each participant. In this way, preservations in particular can be interpreted more accurately.
2. Scanning patients using fMRI could provide insights into the functionality of remnant hippocampal tissue and aid in interpreting preservations.
3. Researchers should make principled predictions about preservations as well as deficits when assessing patients with focal bilateral hippocampal damage.
4. Putting a spotlight on preservations has revealed gaps in our knowledge, for example, concerning verbal memory, that need to be pursued.
5. If we understand more about preservation following hippocampal damage, we may be better placed to approach rehabilitation in a more efficacious way in the future.

6. We believe that the scene construction theory is currently in the best position to account for the patterns of preservation and impairments observed following focal bilateral hippocampal damage. But how is scene construction realized by the hippocampus, and what are the mechanisms involved?

DISCLOSURE STATEMENT

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