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Case studies continue to illuminate the cognitive neuroscience of memory

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The current ubiquity of functional neuroimaging studies, and the importance they have had in elucidating brain function, obscures the fact that much of what we know about brain–behavior relationships derives largely from the study of single- and multiple-patient cases. A major goal of the present review is to describe how single cases continue to uniquely and critically contribute to cognitive neuroscience theory. With several recent examples from the literature, we demonstrate that single cases can both challenge accepted dogma and generate hypotheses and theories that steer the field in new directions. We discuss recent findings from case studies that specify critical functions of the hippocampus in episodic memory and recollection, and clarify its role in nonmnemonic abilities. Although we focus on the hippocampus, we discuss other regions and the occurrence of new associative learning, as well as the involvement of the ventromedial prefrontal and parietal cortices in memory encoding and retrieval. We also describe ways of dealing with the shortcomings of case studies, and emphasize the partnership of patient and neuroimaging methods in constraining neurocognitive models of memory.

Keywords: case study method; amnesia; memory; hippocampus; ventromedial prefrontal cortex; parietal cortex

Introduction

> Always in life an idea starts small, it is only a sapling idea . . . an idea so big it could have grown thirty meters through the dark canopy of leaves and touched the face of the sky.
>
> —Bryce Courtenay, *The Power of One*

From time totime, neuropsychological researchers are fortunate to make contact with an individual whose symptoms following brain damage are startling and illuminating by virtue of his/her presentation of a unique pattern of spared and impaired abilities. Single cases have the potential to confirm a prediction from cognitive theory that otherwise could not be put to the test or that might not conform to theoretical models of the day, thus offering strong challenges to them. From small observations initially based on casual interactions with a patient, entirely new empirical and theoretical ideas can be generated. Historically, it seems that some researchers and clinicians have been somehow primed to look for novel patterns and behaviors, as may have been the case for Paul Broca when he demonstrated the localization of speech, similar to lesser known observations made by Marc Dax,[3] on the basis of observations of his patient Tan,[1,2] or for Scoville and Milner,[4] who reported on the amnesic case of Henry Gustav Molaison (H.M.) after witnessing several other cases of memory impairment following less extensive medial temporal lobe (MTL) resections.[5] What was it that made these cases thrive in a forest of other such cases? Perhaps what is needed is a clear theory that can cultivate and cast light on what is observed, together with an individual with a clear pattern of spared and impaired abilities who, in turn, casts a long shadow over the field.

Since the studies of Broca's patient Tan, single- and multiple-case studies have been instrumental

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in laying the foundation for modern cognitive neuroscience. In the area of memory, for example, the seminal report on H.M.[4] occurred at a time when the theoretical bed was prepared to receive this paper and helped to usher in the modern era of memory research and theory; it continues to exert its influence today.[6,7] The case of H.M. quickly gained the attention of the scientific community as a "pure" case of amnesia. H.M. had suffered from a severe form of temporal lobe epilepsy (TLE) that was rather unresponsive to medication. The most effective treatment option seemed to be surgical removal of the brain areas that were the main source of his epileptic seizures, particularly structures within his MTLs and part of his temporal neocortex bilaterally.[7,8] Yet, the overall extensive nature of the surgical procedure in H.M. did not seem to appreciably affect conclusions regarding the link between MTL function and memory.

H.M.'s rise to prominence on the scientific stage may have had as much to do with how his case was related to major theoretical developments in memory research of the time as with the experimental and extreme nature of the surgery performed on him. The finding that severe memory loss could follow damage to a relatively circumscribed brain region challenged Karl Lashley's strong antilocalization views based on his failure to isolate the engram.[9] Because H.M.'s long-term memory (LTM) alone was impaired, leaving sensory and short-term memory (STM) relatively preserved, his case provided strong evidence against the idea that memory is unitary, and instead lent impetus to George Miller's assertion,[10] and later Sperling's finding,[11] that STM and LTM (James' primary and secondary memory) differ from one another in terms of capacity, among other attributes. The opposite dissociation of impaired STM but intact LTM was needed to challenge modal models of memory that viewed STM as the necessary entryway into LTM. This dissociation was provided by cases such as J.B. and K.F. who presented with impaired verbal/auditory STM and relatively intact LTM.[12,13] Interestingly, these cases were initially treated as conduction aphasics and, according to the theory of the day, were considered to have difficulties with repetition and not with memory per se.

Patterns of impaired and preserved function noted in H.M. also derived from an interest in consolidation—the idea that it takes time and experience for memories to be represented relatively permanently so that they are not susceptible to the effects of interference or noxious agents ranging from lesions to drugs. Interest in consolidation began with clinical observations by Ribot[14] and Korsakoff,[15] and was followed by seminal experimental work by Müller and Pilzecker on nonsense syllable learning.[16] Interest continued into the late 1940s with animal research on cell assemblies[17] and reports of temporally graded retrograde amnesia by Russell and Nathan[18]—memories acquired closer to the time of lesion onset being more impaired than those acquired long before lesion onset. Initial observations in H.M. confirmed this pattern of severely impaired anterograde memory loss with temporally graded retrograde amnesia, lending support to the neural basis of memory consolidation, such that the MTL, and hippocampus more specifically, plays a specialized but temporary role in supporting memory until it is represented (consolidated) in the neocortex without hippocampal support.[19] Studies on another patient in the Penfield and Milner series, someone who had undergone multiple MTL resections, confirmed that damage to the hippocampus needs to extend beyond the uncus in order to induce severe anterograde amnesia, and the more posterior the lesion, the more extensive the retrograde amnesia.[5,20]

Other research with H.M. fueled the multiple memory systems view in specifying that only declarative (explicit) memory for consciously accessible information is at risk of being disrupted following MTL damage; nondeclarative (implicit) memory can be spared in amnesia, indicated by a change in behavior due to earlier exposure to an item (priming) or practice of a skill (procedural memory) without conscious recollection of the learning episode. One of the first empirical studies of H.M. demonstrated spared procedural (motor skill) learning as indicated by H.M.'s improved ability to trace a shape while viewing his hand in a mirror without ever becoming aware that he had performed the task previously.[21] This was complemented by a demonstration in amnesic patients of speeded identification of word and picture fragments after repeated exposure,[22] although the results were originally interpreted by the authors as an instance of declarative memory that was aided by reduction of interference that the fragment cues provided. These patient studies coincided with findings of priming in

nonamnesic participants,[23] resulting in a host of additional studies on the topic in amnesic and nonamnesic populations.[24–28]

There is no doubt that H.M.'s case was eye opening in many ways. The question of interest here is whether there are more recent cases that have significantly influenced the field of cognitive neuroscience, and of our understanding of how memory is represented in the brain in particular, given the proliferation of neuroimaging methods. To argue for the continued value of single-case studies, we present four recent advances in our understanding of memory that we believe would not have been possible without the careful examination of individuals with unique patterns of spared and impaired function following a neurological event. These studies speak not only to the functional organization of memory but, as with the studies of H.M., they have implications about its functional neuroanatomy. Indeed, the first two theoretical advances concern the functional neuroanatomy of declarative memory and the existence of dissociable components, namely episodic and semantic memory and associated recollection and familiarity processes, respectively. The third advance relates to seemingly complementary patient and neuroimaging findings of a role for the MTL beyond memory, including perceptual processes, episodic future thinking, and theory of mind (ToM). However, in the case of future imagining and ToM, it is the examination of preserved function that has helped to constrain theories of MTL contributions to these nonmnemonic functions. The fourth advance also derives from findings of preserved function in MTL amnesia, but concerns the conditions under which acquisition of arbitrary associations is possible independently of the hippocampus. For reference, Table 1 describes individual amnesic cases that made possible these and several other recent advances in memory theory.

Some of these advances highlight the importance of converging methodologies, which we also discuss. For example, when inferences are based on findings of preserved function, scanning of patients with functional neuroimaging can reveal the viability of remaining hippocampal/MTL tissue in supporting those areas of preserved function versus reliance on compensatory strategies supported by brain structures outside of the MTL.[29–32] We also describe other ways of dealing with the obvious shortcomings of single-case methods. Grouping patients together might reduce potential confounds but might also mask variables of interest, suggesting that even patients comprising a large group should be considered on an individual basis as a multiple-case study.[33] In addition, we discuss how lesion and neuroimaging methods are best viewed as being interdependent, providing converging evidence when needed, but also mutually guiding each other in advancing the field, particularly when findings diverge. We end by discussing how single- and multiple-case studies contribute information about two other regions, the ventromedial prefrontal cortex (vmPFC) and the posterior parietal cortex (PPC), which have received much attention recently for their role in memory.

Theoretical advances inspired by individual case studies in memory

The hippocampus and multiple declarative memory systems

Since the time of H.M. there have been other cases that have illuminated our understanding of memory and the brain, including the case of another amnesic person known by the initials K.C. K.C. is perhaps best known for providing strong support for a distinction within declarative memory, proposed by Endel Tulving in the early 1970s and already noted in several group studies of patients.[34,35] Tulving suggested that declarative memory itself is not unitary and may be divided into episodic and semantic components.[36,37] In simple terms, episodic memory is "memory for *personally experienced events* or *remembering* what happened where and when," whereas semantic memory is "memory for general facts of the world."[38] An early case study by Warrington and Sanders showed that retrograde amnesia can be severe and of long duration following MTL lesions, affecting recent and remote memory equally, but did not emphasize the distinction between episodic and semantic memory. Complementary research in Korsakoff patients indicated that the impairment can be limited to episodic (autobiographical) memory.[34,35] An opposite dissociation of impaired semantic memory but preserved episodic memory had also been documented in single cases.[39,40] Observations of K.C. helped strengthen these ideas and return them to prominence.[41] K.C.'s retrograde memory for his personal past was virtually wiped clean as a result

Table 1. A selective list of single amnesic cases described in the literature from 2009 to 2014, along with etiology, lesion description, and notable recent contribution(s) to the cognitive neuroscience of memory

Patient initials	Etiology	Lesion				Contribution	
		H	HC	HC+	EHS	Study	Description of findings
H.M.	Temporal lobe resection	B	B	B		Annese *et al.*[6] (2014)	Detailed histological examination and 3D microscopic reconstruction of H.M.'s brain, allowing for continued retrospective studies.
K.C.	Traumatic brain injury	B	B	B		Rosenbaum *et al.*[110] (2009)	Impaired imagining of past events and semantic narratives.
						Davidson *et al.*[113] (2012)[a]	Reduced social network.
						Kwan *et al.*[109] (2012)	Impaired future imagining but preserved delay discounting.
						Kwan *et al.*[60] (2013)[a]	Extension of above, with additional findings of intact probability discounting and evidence of past- and future-oriented time perspective.
						Ryan *et al.*[167] (2013)[a]	Impaired transverse patterning of abstract and known stimuli with unknown relations, even with unitization strategy.
M.R.	Carbon monoxide poisoning	B		B		Gomez *et al.*[50] (2012)	Impaired spatial encoding based on egocentric updating (possibly relating to path integration) but intact spatial encoding of allocentric relations.
E.P.	Encephalitis	B	B	b-B		Insausti *et al.*[58] (2013)	Data reported from previous studies. The novelty of this study was the detailed histological examination.
M.N.N.	Colloid cyst removal				B	Tsivilis *et al.*[83] (2008)	Bilateral fornix damage leading to anterograde amnesia, highlighting the critical role of the fornix as part of the EHS supporting episodic memory.
S.I.R.					B		
P.A.N.					B		
N.B.	Temporal lobe resection		L			Bowles *et al.*[96] (2010)[a]	Impaired familiarity but intact recollection of verbal material contrasted with an opposite pattern of impaired and intact performance in hippocampal amnesia, representing a double dissociation.
						Bowles *et al.*[29] (2011)	Intact activation of the hippocampus and remaining perirhinal cortex in response to novel stimuli as revealed with fMRI.
						Martin *et al.*[97] (2011)	Impaired familiarity and intact recollection of verbal material (pronounceable nonwords); intact familiarity and recollection of nonverbal material (abstract pictures, faces).

Continued

Table 1. *Continued*

Patient initials	Etiology	Lesion				Contribution	
		H	HC	HC+	EHS	Study	Description of findings
						Köhler *et al.*[98] (2013)	Impaired familiarity of living and nonliving things based on lifetime experience.
R.F.R./ MTL2		B	B	R		Barense *et al.*[104] (2012a)[a]	Impaired discrimination of object feature conjunctions with increasing interference between shared features across multiple consecutive trials, unlikely due to differences in task difficulty.
						Barense *et al.*[233] (2012b)[a]	Abnormal pattern of performance on classic figure-ground perceptual tasks due to reliance on individual parts, believed to be due to perirhinal cortex damage based on comparisons with patients HC2 and HC3 who did not differ from controls.
						Erez *et al.*[122] (2013)[a]	Eye movement data indicating that impaired discrimination of objects (novel and familiar), faces, and scenes with overlapping features or from different viewpoints is not due to abnormal viewing patterns.
						Ryan *et al.*[167] (2013)[a]	Impaired transverse patterning of abstract and known stimuli with unknown relations, even with unitization strategy.
G.P.	Encephalitis	B	B	B		Squire *et al.*[234] (2010)[a,b]	Temporally graded retrograde amnesia for autobiographical episodic and semantic details; intact imagining of future episodic but not semantic details.
						Jeneson *et al.*[235] (2010)[a,b]	Intact working memory for relational information (object–location associations); decline in performance with larger set sizes interpreted in the context of impaired long-term memory.
						Knutson *et al.*[124] (2012)[a,b]	Intact discrimination of objects with high degree of feature overlap and perceptual similarity; decline in performance with increasing difficulty interpreted in the context of impaired long-term memory.
M.C.	Possible status epilepticus and anoxia	B				Andelman *et al.*[111] (2010)	Anterograde amnesia and temporally graded retrograde amnesia for autobiographical episodic and semantic details and spatial navigation.

Continued

Table 1. *Continued*

Patient initials	Etiology	Lesion				Contribution	
		H	HC	HC+	EHS	Study	Description of findings
							Impaired imagining of future personal events (beyond days); intact imagining of future nonpersonal events.
D.A.	Encephalitis	l-R	l-R	R		Roy and Park[236] (2010)	Intact learning of novel complex tool use. Impaired recall of tool attributes, grasping, and skilled use improved with structured cueing.
						Chau *et al.*[237] (2011)	No difference in search times for novel versus repeated target objects embedded in scenes in a flicker change detection paradigm.
						Davidson *et al.*[113] (2012)[a]	Reduced social network.
						Ryan *et al.*[167] (2013)[a]	Intact transverse patterning of known objects and shapes via self-implemented unitization strategy.
						Kwan *et al.*[60] (2013)[a]	Impaired future imagining but intact delay and probability discounting; evidence of past- and future-oriented time perspective.
D.G.	Anoxia	B?				Kwan *et al.*[60] (2013)[a]	Impaired future imagining but intact delay and probability discounting; evidence of past- and future-oriented time perspective.
M.L.	Traumatic brain injury			r		Levine *et al.*[155] (2009)	Impaired recollection of prospectively collected autobiographical events associated with reduced activation of midline brain regions.
A.D.F./ D.A.	Colloid cyst removal	L	L	l	B	Sharon *et al.*[166] (2010)[a]	Intact rapid learning of novel associations in declarative memory via incidental encoding ("fast mapping") but not explicit encoding.
						Waidergoren *et al.*[101] (2012)	Impaired retrograde recollection but intact familiarity of famous names in semantic memory.
E.C.	Encephalitis	B	B			Sharon *et al.*[166] (2010)[a]	Intact rapid learning of novel associations in declarative memory via incidental encoding ("fast mapping") but not explicit encoding.
						Waidergoren *et al.*[101] (2012)	Impaired retrograde and anterograde recollection but intact familiarity of famous names in semantic memory.

Continued

Table 1. *Continued*

Patient initials	Etiology	Lesion				Contribution	
		H	HC	HC+	EHS	Study	Description of findings
P01	Meningo-cephalitis and recurrent meningitis	B	B			Mullally *et al.*[30] (2012)	Unique finding of intact scene construction explained by activation of residual hippocampal tissue.

Note: The list of patients is not exhaustive and is limited to patients with organic amnesia acquired in adulthood. The order in which the cases are presented in the table generally follows the order in which they are first mentioned in the text. Cases from multiple case studies are included as indicated if they are clearly identified based on a unique attribute or pattern of performance and/or if they were reported in multiple independent publications.

[a]Tested within the context of a multiple case study.

[b]Studied together with a group of patients with damage relatively restricted to the hippocampal formation who demonstrated similar patterns of performance.

H, hippocampal formation; HC, hippocampal complex; HC+, lesions extending beyond HC to neocortex; EHS, lesions to the extended hippocampal system (EHS), including the fornix, mammillary bodies, anterior nucleus of the thalamus; B, large bilateral lesion; b, small bilateral lesion; L,R, side of large unilateral lesion; l,r, side of small unilateral lesion.

of a severe head injury, in relative isolation from preserved memory for facts about himself and the world that he had learned prior to his injury. As was discovered years later, even H.M.'s memories for personal events that took place as far back as childhood, which were initially thought to be preserved, were found to be severely impoverished when more careful interviewing and scoring methods were applied. However, similar to other patients, such as H.M., K.C. retained semantic memories that he had acquired in his early years.[7,42]

These and other individual cases of severe and extensive (ungraded) retrograde memory loss for episodic details were instrumental in forcing a reevaluation of the long-standing standard consolidation theory (SCT) and its core prediction that all declarative memories become independent of the hippocampus/MTL over time.[43,44] Observations in these patients led to a significant theoretical departure from SCT and the development of the multiple trace theory (MTT). MTT views hippocampal–neocortical interactions as essential for vivid, detailed reexperiencing of episodic memories for as long as those memories exist.[45,46] By contrast, semantic memories are believed to be formed independently of the hippocampus or to emerge from the gradual abstraction in the neocortex of commonalities and, consequently, are less affected by hippocampal damage.

On the basis of observations in patients, MTT stimulated a multitude of patient[47–53] and neuroimaging studies[54–56] that, in turn, helped to further refine the theory.[46] Continuing debate on the topic is centered on single cases and whether the severe and extensive retrograde amnesia for episodic information seen in some cases is the result of damage that extends beyond the hippocampus/MTL into neocortical regions, as in the case of K.C. Findings based on various single cases followed by Larry Squire and colleagues suggested that this may be the case. At one extreme, the anoxic case of R.B., with very limited damage to the CA1 subfield of the hippocampus, had temporally graded retrograde amnesia for both episodic and semantic information.[57] At the other extreme, the encephalitic case of E.P. with extensive damage to the MTL and lateral temporal cortex bilaterally, recently confirmed on histological exam,[58] was described as having more severe memory impairment overall, although remote autobiographical episodic memories were reportedly preserved, even when sensitive testing measures were used.[59] However, equally sensitive measures have been used to test other cases with selective hippocampal lesions. The results indicate severe deficits in recollecting episodic details for a lifetime of events,[53,60] even when the damage is limited to the CA1 subfields[61] or fornix, as in the single case of A.D.F.[49] Consistent with these findings, functional

magnetic resonance imaging (fMRI) studies on autobiographical memory continue to show that MTL activation is equivalent for recent and remote events, whether unique or repeated, as long as they retain a vivid, experiential component.[62–64]

Recognition and the shift from memory systems to processes

Work with amnesic cases supported another distinction in memory that has been viewed as a parallel to that between episodic and semantic memory (but see below) and relates more to the way that information is processed at the time of retrieval. In a number of cases, the extent of impairment appears to differ depending on how retrieval is assessed, with performance on tests of recall being far worse than performance on tests of recognition[65–67] (for examples in developmental amnesia, see Refs. 68 and 69).

The difference between recall and recognition was informed by a distinction in memory that was first described in the writings of William James,[70] and then elaborated by Tulving[37] and decades of research in cognitive psychology. These studies showed that decisions at recognition of whether a presented item was previously encountered may be made on the basis of either of two component processes: *recollection*, which refers to the experience of remembering specific details of the study episode that had been associated with the target stimulus, and *familiarity*, which refers to a feeling of knowing that a target stimulus had been encountered in the past.[37,71–74] Unlike recognition, the ability to recall an item from memory is believed to depend primarily on recollection, though here, too, a familiarity component may be implicated.[75] It follows that the difference between impaired recall and relatively preserved recognition reflects correspondingly low levels of recollection and yet normal familiarity of recognized items and events.

Interest in the neural basis of recollection versus familiarity followed the cognitive study of recognition memory distinctions and is yet another instance of theory inspiring research in patient cases. The theory that was already in place was grounded in animal research suggesting that, within the context of an extended hippocampal system, the hippocampus plays a crucial role in recollection and the surrounding parahippocampal cortices support familiarity[76] (Fig. 1).[77] Structures that provide major input to the hippocampus, most notably the perirhinal cortex, which also provides input to the dorsomedial nucleus of the thalamus, are thought to be involved in processing an individual item's familiarity. In contrast, pathways and structures that receive hippocampal output within the diencephalon, including the fornix, mammillary bodies, and anterior thalamic nuclei, are thought to carry on the role of the hippocampus in relating items together in memory and recollecting them.

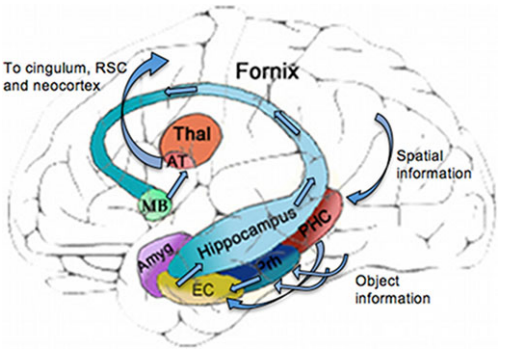

Figure 1. A schematic representation of the extended hippocampal system. Spatial and object information converge into the parahippocampal and perirhinal cortices, respectively, and are relayed to the hippocampus through the entorhinal cortex. Object in context information is then transmitted through the fornix to the mammillary bodies, and through the mammillothalamic tract to the anterior thalamic nuclei. From that point, the system becomes more diffuse, but much of the information is relayed through the cingulum to the retrosplenial cortex and to frontal and posterior neocortical structures, as well as back to the hippocampus. Single-case studies of patients with either fornix, mammillary body, or anterior thalamic damage were critical in providing support for this hypothesis in humans. Amyg, amygdala; AT, anterior thalamus; EC, entorhinal cortex; MB, mammillary bodies; PHC, parahippocampal cortex; Prh, perirhinal cortex; RSC, retrosplenial cortex; Thal, thalamus.

Recent single- and multiple-case studies have provided evidence that largely confirms the predictions of this model, echoing early studies from the 1980s and 1990s,[78,79] although other groups reported contradictory evidence. Confirmatory evidence has come from developmental amnesic cases, such as those of Jon[68,80] and H.C.,[81] and multiple-case and group studies of adult-onset amnesic patients with relatively selective lesions of the hippocampus[79,82] and fornix.[83,84] This included the single case of A.D.F., who showed a similar distinction between impaired recollection and intact familiarity in retrograde memory[53] (see also Ref. 85). These studies provided important causal evidence (in humans) in

support of dual-process models (but see discussion below about inferring causation from patient studies). However, despite similar methods, several other multiple-case and group studies of hippocampal amnesic patients have produced contradictory evidence that appears to favor single-process (strength-based) theories.[86,87] Studies of patients with selective diencephalic lesions likewise have produced mixed results.[83,88,89] Nevertheless, current debate would remain unresolved with or without hippocampal amnesic cases because the core controversy is whether dissociations between recollection and familiarity reflect qualitative or quantitative differences. This cannot be resolved on the basis of findings from larger patient groups with focal hippocampal damage or neuroimaging,[90,91] or even a combination of the two.[92]

What was missing was evidence of an opposite dissociation: impaired familiarity with intact recollection. Although such a dissociation was reported in group studies of Parkinson disease patients,[93,94] the most compelling evidence was provided by a unique case, N.B., whose lesions could be specified precisely and related to the pattern of spared and impaired function. N.B. underwent an unusual anterior temporal lobe (ATL) resection that included a large portion of her left perirhinal cortex but spared her hippocampus; she thereby provided the necessary and very striking evidence to distinguish between single- and dual-process accounts.[95] Across four different experiments, N.B. showed a consistent pattern of impaired familiarity with intact recollection on verbal recognition measures. This was contrasted with an opposite pattern of impaired recollection but intact familiarity on the same measures in TLE patients who underwent a more typical ATL resection that included the hippocampus, thereby fulfilling the requirements of a double dissociation.[96]

Continued research with N.B. has added to our understanding of segregation of function within the MTL, indicating that familiarity processes supported by the perirhinal cortex are material-specific, with verbal, but not visual, material affected by N.B.'s left-sided lesion,[97] and extend beyond the laboratory setting to lifetime familiarity.[98] An fMRI study of N.B. has further revealed that remaining tissue in her hippocampus and MTL cortices produces normal novelty responses.[29] The cases of N.B. and other individuals who have selective bilateral fornix lesions[49,83] are unique because they reflect instances in which information from single cases provides strong evidence not only for the "fractionation" of mind, but also for functional localization. The convergence of specific neurocognitive deficits, highly localized neural damage, and a strong theoretical framework are particularly useful for moving cognitive neuroscience forward on the basis of single-case reports.

Beyond simply supporting or refuting competing theories of recollection versus familiarity, case studies have served to refine the theories and reconcile them with separate evidence of dissociable roles of MTL structures in perceptual processing. Recent fMRI findings of face-specific familiarity signals in perirhinal cortex and scene-specific familiarity signals in parahippocampal cortex detected with multivoxel pattern analysis (MVPA)[99] further bridge the two literatures on recollection versus familiarity and category-specific perceptual processing of items within dissociable MTL regions. Other single-case research emphasizes a critical role for these regions in recollection-like processes during semantic recognition of public events and personalities,[100–103] suggesting that the recollection–familiarity distinction may in fact be orthogonal to the distinction between episodic and semantic memory, a hypothesis that, if confirmed, would have far-reaching theoretical implications.

Nonmnemonic effects of memory structures of the brain

As illustrated in the previous section, findings from individual cases encouraged recent major developments in the cognitive neuroscience of memory, including a shift from the traditional view of the hippocampus as a system that is dedicated to the encoding and temporary maintenance of long-term declarative memory. One possibility is that the MTL is involved in scene construction or in relational processing, which might explain findings of impairment not only in recollection, but also in some aspects of perception,[104] working memory,[105] as well as language,[106–108] future imagining,[60,109–111] and social interaction,[112–115] which were long-believed to be outside the domain of MTL function. The question remains, however, whether such MTL involvement depends on recruitment of MTL-mediated LTM to these tasks, or whether truly nonmnemonic functions of MTL are implicated.

Recently described cases of MTL amnesia have been informative not only of what a brain region does on the basis of findings of impaired performance, but also what a brain region does not do on the basis of preserved performance, which is difficult, if not impossible, to capture with current neuroimaging methods. A focus on areas of preservation has helped constrain theories of MTL involvement in nonmnemonic abilities, providing insight into the nature and limits of the role of the MTL in future decision making[60,109] and theory of mind,[32,114,116] areas that are beginning to be heavily investigated.[117,118]

The MTL and perception. Several multiple-case and group studies of patients have been critical in extending the representational–hierarchical account of MTL organization. This major turn in the understanding of the organization of cognition in the brain occurred on the basis of animal research showing that MTL regions surrounding the hippocampus make unique contributions to perception,[119–121] challenging traditional boundaries between domains such as memory and perception. By this scheme, the perirhinal cortex is considered an extension of the ventral visual stream in representing complex conjunctions of features so that they may be perceived as objects and faces, while the hippocampus represents scenes. Recent case investigations specify that the difficulty for patients with lesions to the hippocampus plus or minus the perirhinal cortex is (1) the result of perceptual interference from overlapping features of objects contained within the array,[104] and (2) may reflect a failure to bind visual information across multiple fixations into a conjunctive percept, as revealed by analysis of the patients' eye movements.[122] It should be noted, however, that studies of perceptual discrimination in MTL amnesic patients has produced discrepant results[104,123,124] that await resolution or alternative interpretations.[125,126]

Future imagining and decision making. Over the past few years, there has been a surge of interest in the role of the hippocampus and episodic memory in the ability to engage in prospective thinking, the seeds of which were the initial observations of K.C.'s inability to imagine future personal experiences.[37,41] These distinctions were later confirmed in the anoxic case of D.B.[127] and in a more systematic investigation of K.C.[110] (first mentioned in Ref. 41, but see Ref. 128). However, it was not until testing of patients with more selective lesions,[111,129] coupled with support from carefully designed fMRI studies[130,131] and framing in the context of alternative accounts of hippocampal function, that these ideas took flight.

Revisiting data from the cases of K.C. and other patients contributed to renewed interest in the reconstructive properties of memory first advocated by Bartlett,[132] later to form the constructive episodic simulation hypothesis.[133,134] The results of patient and fMRI studies were taken to suggest that the MTL serves a flexible role, not only in retrieving details, but also in relating elements of one's episodic memories in novel ways to create representations that may be used when making plans and decisions for oneself and for others (see also Refs. 135 and 136). This is supported by very recent evidence from multiple-case and group studies of patients with MTL lesions of compromised performance on tests of open-ended problem solving,[137] free association,[138] and verbal and figural creativity[139] that place heavy demands on (re)constructive processes and require flexibility in relating disparate details.

The scene construction and self-projection accounts emphasized MTL involvement as part of the default network of common brain regions that underlies not only episodic memory and future imagining but also spatial memory and the ability to infer other people's thoughts and feelings during ToM.[140–143] On the basis of this overlap, one might predict that these abilities would be impaired together in amnesic patients with MTL lesions. However, a different story emerges when one observes and interacts with individual amnesic cases. That was the case for spatial memory, where initial observations in H.M., and several other cases, indicated intact navigation in neighborhoods learned many years before the onset of amnesia,[21,144] despite classic theories of hippocampal function,[145] backed by neuroimaging findings,[146] that would have predicted otherwise. More systematic testing in amnesic patients followed and confirmed that at least some aspects of remote spatial memory are spared in patients following hippocampal damage.[144,147–149]

Unlike remote spatial memory, the role of the hippocampus in future imagining has received complementary support from neuroimaging and patient

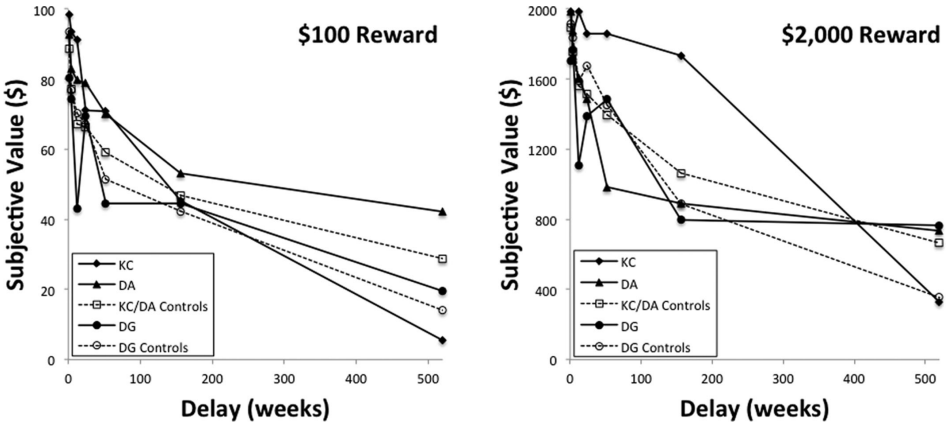

Figure 2. Subjective value as a function of delay in the amnesic cases of K.C., D.A., and D.G., and their respective control groups (dashed line with squares represents discounting curve of controls matched in age and education to K.C. and D.A.; dashed line with circles represents discounting curve of controls matched in age and education to D.G.). The left panel depicts the discounting of the $100 delayed reward, and the right panel depicts the discounting of the $2000 delayed reward.

studies.[134] Nevertheless, recent research involving single amnesic cases has demonstrated that just as there are multiple forms of declarative memory, there are likely multiple forms of future thinking and decision making, with only some forms affected by MTL damage. The ability to choose between smaller, immediate rewards and larger, later rewards is a fundamental aspect of future-oriented decision making and one that is plausibly influenced by the ability to imagine one's possible future.[150–152] However, results of studies investigating delay discounting in K.C. and three other MTL amnesic cases, presented in Figure 2, suggest that the ability to evaluate future consequences does not require MTL integrity and can occur in the absence of the ability to construct imagined future events.[60,109] The amnesic cases further showed a "magnitude effect" (shallower discounting of a larger compared to smaller delayed amount), a standard finding in the delay-discounting literature that appears to be uniquely human.[153] In the absence of the ability to imagine using future rewards, however, it is possible that the patients' decision making was qualitatively different from that of controls.

Theory of mind. Findings of shared activation of the MTL and other brain regions underlying episodic memory and ToM,[140–153] along with simulation theories based on comparable fMRI evidence, led to the prediction that both must be impaired in patients with MTL lesions. This prediction, however, was not confirmed at the level of the individual patient. Indeed, anyone who has ever worked closely with a person with hippocampal amnesia has likely noticed that, like the person's ability to navigate in old environments, his/her ability to read the intentions of others and respond to their needs, at least in the present moment, seems relatively preserved.[32]

This anecdotal observation was confirmed in experiments on ToM in K.C., in a second person, known as M.L., with severe retrograde episodic memory loss,[154,155] and in the developmental amnesic case of H.C., who experienced early-onset hippocampal volume reduction in relation to premature birth.[32,116] The performance of each individual case was indistinguishable from that of controls on a variety of standard tests that are known to be sensitive to ToM impairment. These results suggest that one need not draw upon episodic memories of one's own past mental states in order to infer the contents of other people's minds. In a series of fMRI studies directly comparing episodic memory and ToM, activation of the MTL was related to the level of detail and vividness of specific recollections and imaginings,[63] as well as to whether the other person in the ToM condition was personally known.[156] This was confirmed in a separate case study of H.C., who was more impaired at imagining the experiences of close others than of people who were unknown to her,[114] just as she was impaired in remembering the past[81] and imagining the future[157] (but see Ref. 158). A possible interpretation of these data is that episodic memory provides a primary, rich source of vivid details and personal facts that

are automatically activated when imagining or predicting the experiences of close others. Importantly, had neuroimaging evidence been relied on alone, a very different conclusion would have emerged regarding the role of episodic memory and MTL function, as the MTL would have been activated in all conditions.

Acquisition of declarative (relational) knowledge independent of the hippocampus

Significant developments have been made in understanding hippocampal and MTL function with respect to the processes they support and their contribution beyond memory. While deficits in other domains can be detected under certain conditions, the hallmark of hippocampal anterograde amnesia, by some accounts, remains a severe deficit in acquisition of new declarative memory, whether it is episodic or semantic. Indeed, the gateway to new semantic memories was presumed to be hippocampally mediated episodic memory. In recent years, however, there have been several case reports demonstrating rudimentary semantic knowledge of facts, faces, words, and places that could only have been acquired after the onset of amnesia, suggesting some preserved declarative learning independent of the hippocampus (but see critique by Squire and Zola).[159] This has been reported even in the most profoundly amnesic cases, such as those of H.M.,[160,161] K.C.,[162] R.F.R.,[163] and E.P. and G.P.[164] The knowledge was consciously accessible by using several kinds of cues, suggesting flexibility and associations with additional knowledge.[160,164]

Investigations of these famous single cases were critical for identifying the possibility of hippocampal-independent declarative learning in everyday life. Naturalistic learning in these patients suggested that neocortical structures might be capable of more learning-induced plasticity than had been suspected by computational and neuroanatomical models of declarative memory. Laboratory studies with some of the same patients have also begun to highlight the conditions that appear to promote such neocortical learning.

As in many other domains, H.M. provided an early clue for the conditions that support hippocampal-independent learning. Capitalizing on H.M.'s known passion for crossword puzzles, Skotko *et al.* devised a test to examine whether new learning can be anchored to old knowledge.[165] They reported that H.M. could solve puzzles that contained postmorbidly learned information and display evidence for preserved knowledge of these new facts, but only if these were presented in the context of premorbid information that he possessed. For example, embedding information about the Salk vaccine (postmorbid information) in the definition of polio (premorbid knowledge) was successfully solved by H.M. and, in the process, supported incidental acquisition of new knowledge. The report emphasized anchoring of new learning to old knowledge, but other characteristics of the paradigm may have also contributed to successful hippocampal-independent learning. Specifically, the task was engaging and involved active discovery of information by H.M. on the basis of his knowledge, and learning was incidental. Combinations of these features appear to support hippocampal-independent declarative learning in two recent case reports.[166,167]

Fast mapping. In a recent study, Sharon *et al.* found that under certain conditions there may be exceptions to the notion that the hippocampus is critical for rapid formation of arbitrary associations, whereas the neocortex is only capable of slow learning. In that study, adult hippocampal amnesics incidentally learned novel arbitrary associations at normal rates through an incidental process called *fast mapping* (FM), but failed to acquire similar associations intentionally.[166] FM is the process by which children infer by exclusion the meaning of new words and that supports later memory for these novel associations even after a single exposure.[168–170] Sharon *et al.* administered an FM task adapted for adults to four patients with dense amnesia, including A.D.F. and E.C., and to matched healthy controls. Patients and controls were told the task was a perceptual task. On each trial, a novel and a familiar picture appeared (e.g., a numbat and zebra), and a simple perceptual yes/no question that contained the novel picture's label (e.g., "Is the numbat's tail pointed upward?"). Participants deduced that "numbat" refers to the novel item and correctly selected it. Sixteen novel associations were presented twice. On a matched standard associative memory task using explicit encoding (EE), a single picture appeared (eliminating the contrast and discovery components believed to underlie the FM mechanism), along with instructions to try to remember

the association between the pictures and their labels (e.g., "remember the tenerec"). Surprisingly, on the FM task, amnesic patients performed as well as controls on associative recognition both after 10 min and after 1 week. By contrast, patients were markedly impaired compared with controls on the EE task. The patients' performance pattern fulfilled the statistical criteria for a classical dissociation between FM and EE functions, demonstrating learning of arbitrary associations after only two short exposures to the picture–label pairs. Importantly, controls performed much better on EE than FM so that task difficulty or depth of processing could not account for the data. In the case of A.D.F., it was also demonstrated that the information gained was declarative in that he was consciously aware of his knowledge and could use it flexibly.

Two patients with left ATL damage were also tested on the task, because the ATL is a central neocortical structure implicated in representation of semantic knowledge.[171–174] As predicted, both these patients failed the FM condition, and one in fact showed better learning through EE than FM, providing evidence for a double dissociation. It was hypothesized that the ATL might be critical for learning through FM. However, these two patients also had damage to MTL neocortical structures (perirhinal and entorhinal cortices), and a model of combined ATL/MTL cortical contributions to FM could not be ruled out. Either way, the finding that learning declarative information can be supported directly by the neocortex is surprising and offers an important exception to theories of declarative memory and neocortical plasticity (but see Ref. 175 for contradictory evidence).

The characteristics of FM learning, which might make it conducive to neocortical semantic memory acquisition, are strikingly similar to those in the study by Skotko *et al.*[165] For one, novel information appears in the context of already known items, possibly supporting the modification of existing semantic schema knowledge. A recent study using schema-based learning in rats[176] has challenged the view that consolidation in the neocortex is slow. Information became hippocampal-independent much faster than previously demonstrated because it was embedded within an existing schema. Unlike FM, however, initial acquisition in that study was still reliant on the hippocampus. Learning through FM is also incidental and requires active discovery on the part of participants; the information is not simply given.

Although FM appears to support direct neocortical declarative learning, the representations it produces may be fragile,[177,178] which may account for the failure of the study by Smith *et al.*[167] to reproduce the results. In a recent study,[179] three amnesic patients, including the encephalitic patient D.A., were able to acquire associations through FM normally, but learning through FM was susceptible to catastrophic interference.[180] Interestingly, the same susceptibility was also observed in healthy controls for FM but not EE associations. It may be that gradual incorporation of articulatory phonetic information used in naming is adaptive in allowing verification and conceptual elaboration, and in preventing erroneous entries from being stored during childhood early learning of conceptual knowledge. Indeed, Medina *et al.*[178] demonstrated that once hypotheses about word meanings are formed during FM, they are maintained unless contrary evidence is encountered. The system then resets, and a novel hypothesis is formed independently of prior experiences with the item. Thus, on the one hand, representations formed through FM are flexible and durable in order to allow comprehension of meanings in different contexts and over prolonged times, but, on the other hand, are fragile to avoid errors in laying down the foundation of knowledge.

Transverse patterning. Patient D.A. with extensive postencephalitic damage and severe amnesia also participated in another case study that challenged the ubiquity of hippocampal involvement in acquisition of relational representations.[167] Although that study took a very different approach—examining patients' abilities to perform transverse patterning (TP) tasks—the principles that appear to support performance are still similar, as discussed below. TP involves situations in which the relative reward values of pairs of items need to be learned (e.g., A > B, B > C, but C > A). Because all items are equally rewarded, to successfully perform on TP tasks one needs a representation of the relationships between all items, an ability that is extremely sensitive to hippocampal dysfunction.[181]

An investigation by Ryan *et al.* was prompted by patient D.A.'s unexpected successful performance on a TP task. When questioned, D.A. eloquently described his strategy during the task, and Ryan

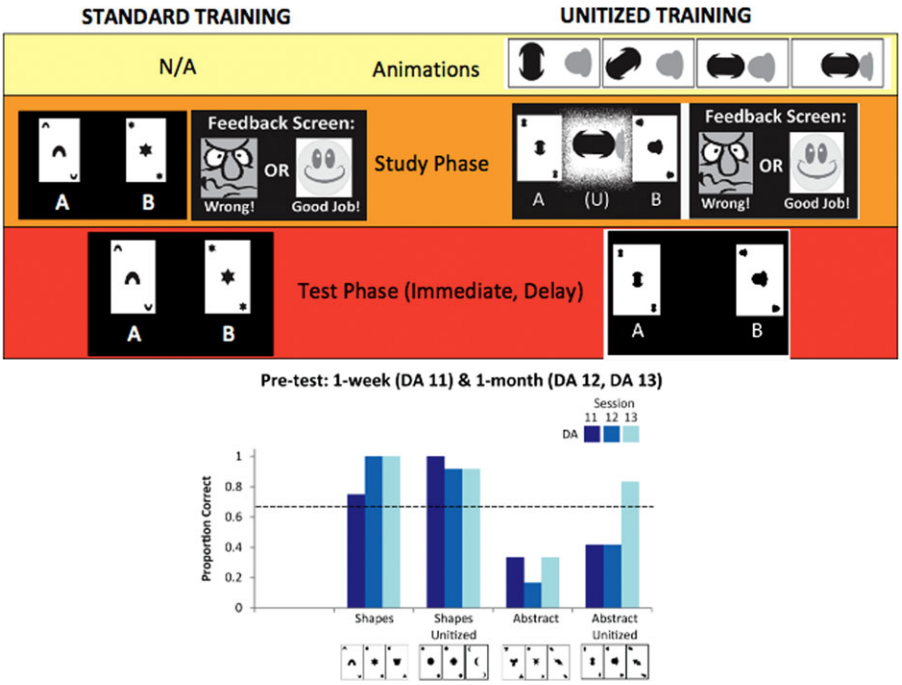

Figure 3. Top (color) panels: transverse patterning training with standard and unitization procedures. Unitization procedures were presented through flash animations depicting one object interacting with another object (e.g., one object piercing another object). During training, a still image showing the final unitized objects was presented along with instructions to use the image to help determine which object wins. The test block was identical to standard training, such that no unitized image was provided. Bottom panel: D.A.'s lasting transverse patterning performance following extended delays of 1 week and 1 month since training. D.A. successfully learned the relations among familiar shapes without preexperimentally known relations in the standard and unitized conditions, both 1 week and 1 month posttraining. Performance in the abstract conditions was poor at 1 week posttraining, but successfully exceeded the 67% elemental maximum (dashed line) at 1 month posttraining.

et al. suspected that he was spontaneously using unitization to compensate for his impaired relational processing.[167] Specifically, D.A. used fused representations of the items, such that the relationship between them could be extracted from the unitized representation instead of being reconstructed each time anew. To give an example, when presented with two abstract shapes, D.A. created interactions between them that would physically entwine the objects (e.g., "blob could cover star's points and dull it"). D.A. could easily perform the TP-based childhood game rock–paper–scissors, which he reported was very familiar to him, and could also perform TP when the stimuli were playing cards and geometric shapes, always using similar strategies (Fig. 3). Critically, D.A. retained the information about the relationship between all item types even at long durations, a month after learning. This suggested that unitization not only formed a fleeting representation of new information about relationships between items, but it produced long-lasting declarative knowledge that could be retrieved again long after the initial acquisition. Interestingly, R.F.R. and K.C., who also participated in the study, could not apply the same strategies, highlighting the importance of considering individual differences in cognitive neuroscience investigations.

This study underscores the point that, while the hippocampus may be critical for creating and reconstructing relations among items, there are other routes through which relational information can be acquired and represented. Given the perceptual and conceptual nature of the representation used by D.A., it is highly likely that the unitized information was created and directly embedded within neocortical networks, although direct evidence for this is lacking. R.F.R.'s and K.C.'s failure to use unitization is proposed to be related to the extensive damage they both have to the left ATL and the prefrontal cortex.[167] This is remarkably similar to the

findings from Sharon *et al.* described above.[166] Also similar to the studies described above are the conditions that promoted hippocampal-independent TP performance and memory. Learning in D.A. was dependent on the availability of prior knowledge both about TP relationships (through rock–paper–scissors) and his ability to name the objects and describe an amalgamated relationship between them. Learning was also incidental and dependent on an interactive and spontaneous problem-solving discovery of the novel to-be-remembered information. Importantly, it took a unique patient, demonstrating a unique preserved ability, and having the capacity to communicate his strategy to support this discovery. Averaging performance across patients in this case would have obscured important patterns of behavior.

Summary

In sum, there is mounting evidence that the MTL is needed for encoding of new, declarative material into LTM and for forming associations, as well as for the continued maintenance of episodic memory. However, new findings based on single cases encourage reexamination of traditional views of how memory is organized in the brain and why it might fail following insult. Although this research is largely still in its early stages and the interpretation of findings is speculative, it already has forced memory scientists and clinicians to hypothesize a broader role for the MTL than its role in memory, namely, the relational binding of details that can support memory for new, flexible associations, which, in turn, form the bedrock for construction and reconstruction. At the same time, although scientists and clinicians tend to focus on the aspects of memory and cognitive function that are lost, neurological disorders are also defined by areas of function that are spared. In the case of MTL amnesia, this includes schemas, which may allow for compensation for areas of impairment in these patients but are as yet ill-defined.

Addressing methodological and conceptual challenges of single-case studies

Traditionally, dissociations have been defined as a patient's performance reflecting a deficit on one task with intact performance on the other. A double dissociation requires the existence of a second patient showing the reverse pattern of performance. When such performance profiles are described, the two cognitive functions are said to be independent of one another. For many years, much of cognitive neuropsychology has focused on describing the architecture of the cognitive system on the one hand, and its underlying functional neuroanatomy on the other, by identifying dissociable cognitive functions and constructing box-and-arrow models of neurocognition.[182] The difficulties with theory and the assumptions pertaining to single-case contributions to understanding the architecture of mind and of mind–brain relationships have been extensively debated for decades.[183–186] A comprehensive discussion of the advantages and limitations of this approach is outside the scope of this review. However, we highlight how recent case studies and case-series reports have dealt with some of the challenges methodologically. For recent, more intricate, theoretical discussions of case studies and case-series studies, see Refs. 187 and 188.

Statistical criteria for identifying dissociations

One methodological and theoretical difficulty that afflicts single-case studies is the criterion used to identify dissociations. A common practice in the field for many decades was to describe patients' scores with respect to the number of standard deviations by which they differ from their control group, essentially assuming a normal distribution of controls' scores and using the *Z*-score statistic. This approach is probably accurate in studies involving large samples of control participants. However, most studies employ small groups of controls and therefore run the risk of overestimating the rarity of a difference in performance, increasing Type I errors. Although some studies still take this approach even with small samples, many studies address this problem by employing more rigorous statistical methodologies, for example, by using nonparametric comparisons, such as setting a cutoff at the lowest control score, use of confidence limits, and using simulations to evaluate significance (for an example, see Ref. 189).

More recently, a set of statistical tools have become available that are specifically designed to allow direct comparisons of single subjects and small comparison samples on the basis of theoretical considerations of double dissociation.[190,191] Studies reviewed here have used such refined statistical methods,

ranging from simpler *t*-test–based procedures[191] that allow for detecting a simple deficit on a particular task[104,109,114,128] to the use of Bayesian statistics[92] to compare differences in regression slopes of retrograde recollection deficits.[101]

Another important methodological advance is the realization that sometimes it is not enough to show a significant difference in scores between a patient and a control sample. On some occasions, the score on the preserved task may not be significantly different from that of controls but may still be numerically lower; in that case, the actual difference in performance on the two tasks may be small and simply falls on two sides of the significance cutoff. Moreover, the frequency with which differences in performance on two tasks may occur in the general population, and the sizes of these differences, are not being considered. An operational definition for dissociation that takes into account the abnormality of the discrepancy between the two scores in the patient compared to the discrepancy between the scores in controls has been used in several studies reported here. When both the absolute score on the target cognitive task and the discrepancy in scores from another cognitive task are statistically significant, the two cognitive tasks are considered dissociable in the strong sense of the word, for example, in showing a specific deficit on working memory measures for unfamiliar compared with familiar stimuli,[110] dissociations between future imagination and future decision making,[60] and dissociations between retrograde recollection and familiarity in semantic recognition.[101] Many of the other studies reported in this review demonstrate classical forms of dissociation, that is, there are significant differences in performance between patients and controls on one task and no significant difference on the other; however, the extent to which the difference score between tasks is abnormal is not tested. It remains unclear whether this is because the strong dissociation hypothesis was never tested or whether it reflects a lack of evidence for strong dissociation in the data.

Addressing inferential limitations of single-case studies

The primary purpose of case studies as practiced in cognitive neuropsychology and cognitive neuroscience is to provide relevant information for theories of the functional organization of the systems underlying human cognition. Very frequently, this may be accompanied by an attempt to localize certain functions, but the constraints provided for models of human cognition are of sufficient interest in and of themselves.[186,188] A central theoretical and practical challenge for single-case studies is dealing with generalization problems. These may arise from issues such as the potential atypical nature of a patient, and from questions about functional unitariness (i.e., whether the observed syndrome is the result of damage to only a single functional subsystem vs. several subsystems).

Examples of how these problems can be addressed can be found in some of the studies reported here. For example, conclusions drawn from a single patient can be supported by the accumulation over time of evidence from multiple cases with similar profiles of behavior and the use of meta-analytic approaches. These can clarify theoretical issues and highlight aberrant results due to individual patient idiosyncrasies. In trying to understand the role of the hippocampus and related MTL structures in remote episodic memory, Nadel and Moscovitch,[45] followed by Fujii *et al.*[43] and Moscovitch *et al.*,[44] reviewed dozens of patients reported in single- and multiple-case studies (see also Table 1). These reviews qualitatively integrated the findings as they pertain to patterns of retrograde amnesia, types of tests used to assess remote memory, and extents of reported lesions. As described earlier, whether or not the hippocampus is needed for retrieval of remote memories is contentious, and each single study can be criticized either for the extent of lesions suffered by the patients[59] or for the methodology of assessing episodic memory.[53] These integrated reviews, however, appear to support the idea that for truly episodic memories, the hippocampus is critical throughout a person's lifetime, and such reviews require that single cases and multiple-case studies are consistently published.

Moreover, personal idiosyncrasies and compensatory strategies may themselves be an object of investigation and highlight important theoretical issues. For example, as mentioned above, in testing the densely amnesic patient D.A. whose hippocampi were damaged, Ryan *et al.*[167] unexpectedly discovered that D.A. could sometimes perform TP tasks, which presumably depend on the hippocampus for relational processing and therefore should have been impaired. Careful analysis of D.A.'s strategy revealed that he was spontaneously using a unitization

approach that bypassed the need for relational processing on the task. By adding conditions that specifically induced unitization, and by testing additional patients, Ryan *et al.* were able to demonstrate that successful performance was indeed dependent on the ability to fuse items into a unitized representation.

Beyond double dissociations

Dissociations are critical for understanding neurocognitive modular processes and their structure. However, comprehensive and more refined theories of memory, which capture its intricate and dynamic nature, require an account of the relationships between these modules, the dynamic processes that make up memory functions, and the relationships between subprocesses. The study described above by Ryan *et al.*[167] is a prime example of such theory-driven investigation that focuses on processes and offers insights into different paths that may support similar behavioral outcomes. Addressing memory processes as reflected in unique neurological cases can be greatly enhanced by investigating multiple cases using a multiple-case or case-series design, rather than a single-case study design, focusing on specific processes and combining single-case studies with other methodologies such as neuroimaging.

Methodological approaches to enhance single- and multiple-case research. Compared with single-case studies, case-series designs are characterized by recruitment of several patients with more heterogeneous neurological characteristics, and often a more focused cognitive investigation that is common across cases. This allows researchers to capitalize on the variability in performance and lesion extent in order to better characterize the relationship between behavior and the brain. In classical case-series approaches, these relationships are characterized more formally using correlation or regression designs, whereas in multiple-case study approaches, this is usually performed more qualitatively by examining the individual patient's patterns of behavior and patterns of lesions. Importantly, both these approaches do not average performance across patients, as is done in group lesion studies, but rather use the individual variability as the object of investigation. The individual patient's data are recoverable rather than hidden by the group. Many of the studies reported here, investigating the roles of MTL cortical areas and the hippocampus in perception, have implicitly taken this approach. These studies typically included only a small number of patients, and the patients' behaviors were examined based on the existence or absence of MTL cortex lesions.

An additional approach to enhance conclusions based on single- and multiple-case research is to combine the patient method with neuroimaging.[192] Several recent high-profile publications have taken the approach of testing patients with focal lesions and either focal cognitive deficits or unexpected preservation to further investigate the cognitive processes involved. This too would not have been possible without the advent of appropriate methodologies for analyzing and interpreting the data. For example, Hassabis *et al.* reported on a case series of patients with hippocampal amnesia who were severely impaired in their ability to imagine scenes.[129] One of the patients (P01) was an obvious outlier, demonstrating intact scene construction despite severe memory impairment and reduced hippocampal volume. Using fMRI, Mullally *et al.*[30] demonstrated that P01's intact scene construction was associated with activation in residual hippocampal tissue. In addition to qualitative inspection of the functional data, these authors also applied adapted statistical methods for single-case comparisons, allowing a quantitative comparison of hippocampal activity. Similarly, Levine *et al.* investigated anterograde autobiographical recollection in M.L., a case described above with focal retrograde amnesia.[155] This allowed them to collect events prospectively for subsequent recollection while being scanned and to have substantial control over the actual details of the events. Using region-of-interest (ROI) and single-case statistics methodologies together with disjunction analyses, they were able to show that M.L.'s impoverished subjective reports of recollection were associated with reduced activity in midline structures that constitute part of the experiential autobiographical neural network.

Other studies have used a small number of single cases to investigate the effects of focal lesions on temporal aspects of cognitive processing using electrophysiology. This combination of methods is particularly useful, as it overcomes one of the major shortcomings of lesion studies—that of limited information on the temporal dynamics of cognitive processing. Addante *et al.*[92] address the controversy of the recollection–familiarity distinction in

recognition memory by investigating event-related potential (ERP) signatures of the two processes in three patients with hippocampal amnesia. By doing so, they capitalized on the well-described components of the ERP that reflect early familiarity (FN400) and late recollection (LPC). Using both group-level comparisons and Bayesian factor analyses, they were able to demonstrate that the patients had intact N400 and no LPC, both as a group and individually. These ERP profiles were compatible with the patients' behavioral recognition performance and with prior research. In another electroencephalogram (EEG) study that probed the role of the vmPFC in retrograde memory retrieval, Gilboa *et al.*[193] tested patients with vmPFC damage for their ability to recognize personally familiar, famous, and nonfamous faces. In this study, the advantage of the temporal specificity of EEG was particularly evident, as patients were lacking an early posterior face familiarity signal (N170) even though their lesions involved anterior structures. Individual differences in performance among the patients were used to demonstrate the relationship between an early ERP component and the ability to make rapid accurate decisions. This combination of methodologies converged to suggest a role for the vmPFC in automatic memory monitoring and its possible relationship to schema representation.

Case studies and non-MTL contributions to memory

Ventromedial prefrontal cortex (vmPFC)

The vmPFC has begun to figure prominently in theories of memory because of its involvement in a variety of memory tasks as evident both in functional neuroimaging studies of memory in humans and in lesion and early gene-expression studies in rodents.[194,195] Particularly noteworthy is the involvement of the vmPFC in remote memory, which led a number of investigators to propose that it is the hub of a network that is implicated in (or simply that it is needed for) assimilating recently acquired information, initially hippocampally dependent, to preexisting schemas, which can then be used to recover those memories independently of the hippocampus. Damage to the vmPFC should, therefore, impair recovery of remote memories, although recent memories may be spared (but see Ref. 196).

How do single- or multiple-case studies of patients with lesions to the vmPFC contribute to this discussion? This question is all the more interesting since damage to the basal forebrain, which includes the vmPFC, has long been known to be associated with confabulation, a fascinating memory disorder first reported in case studies that, at first glance, would seem not to be the type of disorder predicted by the proposed function of the vmPFC in remote memory.[197–199] Typically caused by aneurysms of the anterior communicating artery (ACoA), which irrigates the basal forebrain, confabulation is "an account based in memory that is false with respect to the context in which the event is placed, and may contain false or grossly inaccurate details within its own context" (see Ref. 209, p. 962). Because the patient is unaware of the deficit and believes in the memory's veracity, Moscovitch dubbed it *honest lying*.[197] Interestingly, theories of confabulation have long posited a relationship between confabulation and aberrant schema functions,[198,200] as well as a central role for vmPFC dysfunction in mediating this relationship.[201,202] Although confabulation is the most prominent memory deficit associated with damage to the vmPFC, it is hardly mentioned by the proponents of remote memory/schema theory because it is difficult to accommodate it with recent existing theories of its function (though see Refs. 194 and 203). We will return to this problem and suggest how single-case/multiple-case studies can address it and inform theories of memory transformation and consolidation after providing some background.

Single- and multiple-case studies were the main contributors to our knowledge about confabulation historically, and continue to be so today.[199] By reviewing all of the existing case studies of confabulation at the time, Gilboa and Moscovitch[204] determined that a lesion to Brodmann area 25 was deemed to be crucial, the same area activated in the fMRI memory studies described above (Fig. 4). Single-case and case-series studies of confabulation have informed cognitive and cognitive neuroscience theories of anterograde memory[197,198,205–209] and have called attention to concepts, such as temporality and felt rightness, which otherwise are not prevalent in the memory literature. Theories on confabulation have also noted that the vmPFC likely plays a similar role in recent memory as it does in remote memory—both types of memory seem to be prone to confabulation to an equal degree, as does semantic memory, at least in the sense of knowledge

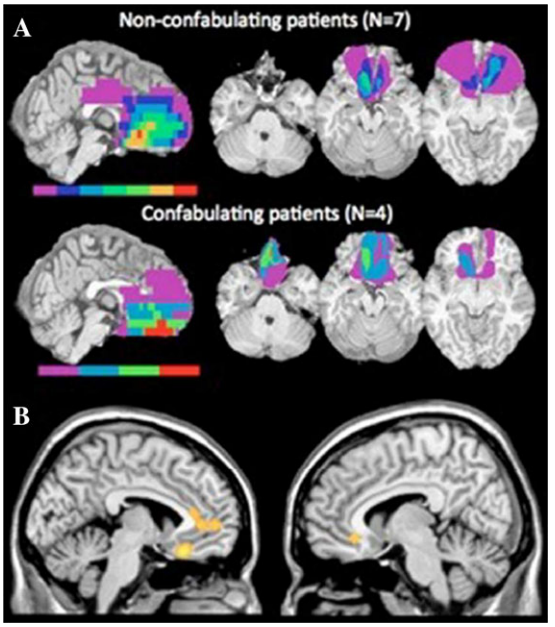

Figure 4. (A) Lesion overlap of nonconfabulating ($n = 7$) and confabulating ($n = 4$) ACoA patients demonstrating maximal overlap of lesions in the most ventral aspect of the vmPFC.[209] Color bars represent the number of patients with lesions to an area, with red indicating the maximal number of patients. (B) Rendering of areas in the vmPFC, reported by four recent fMRI studies of schema and memory,[194,215,231] using the Activation Likelihood Estimation (ALE) algorithm. ALE analysis was conducted using the standard settings in the Ginger ALE 2.1 software.[232] The test was corrected for multiple comparisons using the false discovery rate (FDR) method with $P < 0.05$, and a minimum volume of 150 mm^3 voxels was used to define a cluster.

of events, people, and semantic narratives, if one queries it appropriately.

Using a multiple-case study approach in which they compared people who had ACoA aneurysms with and without confabulation, Gilboa *et al.* found that all of them performed poorly on a test of temporal context confusion.[210] Whereas controls could withhold making old responses to items that were targets at time 1, but served as lures at time 2, all the ACoA patients, including the nonconfabulators, made significant false alarms to the previous targets. Likewise, they responded to targets at time 2 that never appeared at time 1, but only bore a visual similarity to them. By contrast, what distinguished confabulators from nonconfabulators were their idiosyncratic choices of implausible (bizarre) alternatives on a recognition test of well-known fairy tales, whereas controls and nonconfabulators confined their errors only to plausible alternatives.

Similar results were reported by Kan in another multiple-case study using the semantic illusion paradigm, which elicits erroneous endorsement of misleading statements (e.g., "Two animals of each kind were brought onto the Ark by Moses before the great flood") despite their knowing the correct answer (e.g., Noah).[211] Monitoring demands were manipulated by varying the semantic overlap between target and foils, ranging from high semantic overlap to unrelated. Increasing the overlap increased endorsement of false related foils in controls and, even more so, in both confabulating and nonconfabulating people with ACoA aneurysms, but only the confabulators endorsed the unrelated items (for other single- and multiple-case studies, see also Refs. 212–214). Single-case studies from Schnider's group, however, have been instrumental in setting the boundary conditions for the postretrieval monitoring hypothesis of confabulation.[199] These studies have shown that confabulation and poor performance on tests of temporal context confusion can coexist with good performance on some executive tests of frontal function, and conversely, poor performance on some executive tests is not associated with confabulation. One conclusion proposed by Kan is that such findings are "consistent with the broader notion that vmPFC is critical for integrating intuitive and analytic aspects of decision making . . . " (see Ref. 211, p. 1014).

How can single-case studies be used to inform the discussion on the role of the vmPFC in remote memory and schema formation/assimilation? First, as Maguire noted,[215] there is a paucity of data on the nature of remote memory deficits in patients with vmPFC lesions, whether they confabulate or not. The existing data suggest that the deficits can affect recent as much as remote memories, whether they are episodic or semantic, given the right conditions. Second, there is a need to determine whether the vmPFC, particularly area 25, is truly involved in evaluating mnemonic and nonmnemonic information;[194] whether it is implicated in representing gist-like information that relies on forming, or selecting, well-constrained schemas;[203,216] whether these functions, or other functions, that both rely on regions of area 25 may be dissociable from one another, with only one implicated in confabulation; or whether another mechanism

entirely, such as the reduction in cholinergic input to the hippocampus following basal forebrain lesions, is responsible for confabulation.[188] Whatever the case, it is clear that researchers will have to turn to single-case or multiple-case studies of patients with lesions because current functional neuroimaging is not capable of predicting the confabulating-type of memory deficit associated with damage to that region.

Posterior parietal cortex (PPC)

Whereas single- and multiple-case studies took the lead in noting the importance of the vmPFC for memory, it was functional neuroimaging data, first from ERP[217] and later from fMRI,[218,219] that alerted researchers to the role that the PPC might play in memory. In a seminal paper, Wagner *et al.*[218] showed that the PPC is very often activated in a variety of episodic memory tasks. Borrowing from studies of the PPC in other domains, they proposed a number of hypotheses to account for this effect, which included the PPC's involvement in attention, working memory, particularly episodic buffers, and in accumulating information for decision making. Investigators refined these proposals and added some of their own (for reviews, see Refs. 220–222), such as the role of the PPC in experiential (phenomenological) aspects of recollection.[223,224]

Single-case and case-series papers on patients with parietal lesions quickly followed and were consistent with some of the predictions based on the proposed hypotheses, but the evidence is not yet good enough to distinguish among them. Berryhill and Olson reported that two patients with bilateral parietal lesions and simultanagnosia also had difficulty in recollection, as evidenced by a paucity of rich perceptual details in their reports of autobiographical memories.[225] The problem they noted was one of retrieval because, when prompted to provide the details, they could do so. Similar impairments in recollection in more traditional laboratory-based studies using the remember/know (R/K) paradigm were reported by Davidson *et al.*,[96] but, interestingly, without impairment in source memory—considered by some to be an objective marker of recollection—compared with the more subjective R/K judgement.

Concurrently, Simons *et al.* reported similar deficits in subjective measures of recollection, such as confidence, but not in accuracy on a variety of tests, with no noticeable difference between patients with bilateral and those with unilateral lesions, whether on the left or on the right side.[223,224] A similar finding was reported in left and right parietal patients' subjective experience associated with navigation—the majority of the patients were impaired at vividly reexperiencing details of the environment in tests of route navigation.[226]

A multiple-case study provided support for the attention to memory (AtoM) account, which states that the superior PPC contributes to the allocation of top-down AtoM, whereas the inferior PPC is primarily implicated in the bottom-up AtoM. Using a paired-associate memory cuing paradigm, Ciaramelli *et al.*[227] found that patients with lesions that included the superior PPC did not benefit, as did controls and patients with ventral parietal lesions, from valid cuing of the correct member of the pairs. By contrast, patients with inferior parietal lesions were disproportionately unable to resolve the deleterious attentional effects of invalid cuing and produced more errors and longer reactions times on those trials. Dobbins *et al.*[228] used a different cuing paradigm by informing participants that the target in the next trial is likely to be "old" or "new." Whereas controls benefited from this advance information, patients with parietal lesions did not. The researchers did not, however, find a difference between patients with superior lesions and those with inferior lesions as the AtoM model predicted, although the variability in performance and the small sample size (three patients in each group) may have prevented that difference from emerging.

Hypotheses regarding the role of the PPC in memory are now sufficiently refined at both a behavioral and neuroanatomical level[220,229] that appropriate single-case and multiple-case, and possibly case-series, studies will help resolve some of the ongoing debates. Indeed, as this review has shown, this is true not only with regard to the PPC but with other regions as well. For example, hypotheses regarding specialization along the long axis of the hippocampus, or among its various neural subfields,[230] are likely to be testable only with single-case studies because cases of lesions confined to these regions are likely to be very rare. Of course, such hypotheses are amenable for testing by fMRI; but, as we will argue below, it is not clear how differences in brain activation are translated into predictions about behavior when such regions are damaged.

The human side of single-case studies

It often is argued that lesion data are necessary to anchor findings from functional neuroimaging studies because the latter are correlational with respect to the involvement of different regions in particular tasks, whereas only lesion data can provide evidence that there is a causal link between the participation of these regions and performance. We do not want to dispute this view, and indeed some of the data we presented, such as the dissociation between episodic memory and ToM and temporal discounting, are cases in point. Although regions implicated in these nonmnemonic aspects of cognition often overlap with those implicated in episodic memory, the fit is not perfect. Single-case studies can uncover dissociations when functional neuroimaging data suggest associations between functions. We believe, however, that this correlational argument is overstated for two reasons. First, careful functional neuroimaging studies using more sophisticated behavioral designs, and some of the latest technological and analytical advances, such as high-resolution, MVPA, and functional connectivity analyses, may also point to dissociations that could not be detected in earlier studies. More importantly, to our knowledge, the evidence suggests strongly that if a particular region is activated, and even correlated with task performance, then instances for which comparable lesion data are available invariably confirm that region's contribution to task performance. Even in the contrary example above, it is likely that some aspects of ToM and temporal discounting will be affected by damage to memory-related regions, as indeed the work of Rosenbaum and her collaborators suggests.[109,114]

Besides, one can argue that even the lesion data are correlational because it is not known whether damage to a particular region is directly related to performance on a particular task or to execution of a particular function, or whether that damage is only correlated with effects that are produced via some other region or some other mechanism. The phenomenon of *diaschesis*, which has been evident since the beginning of scientific neurology, speaks to this issue. Indeed, Hughlings Jackson long ago warned that one cannot infer function of a neural structure from the impairments one observes following its damage.

With these provisos in mind, we still wish to argue that lesion data, and especially data from individual cases, are necessary to extrapolate, or relate, brain activity to function and behavior in ways that are not apparent from the neuroimaging data alone. In the remainder of the paper, we shall focus on some examples that illustrate different aspects of our argument.

We noted that the lateral frontal cortex and PPC are as ubiquitously activated during retrieval of episodic memories as the MTL itself. From these data, one could not predict what the effects that damage to each of these three regions would have on behavior. It is not, simply, that their effects on behavior are epiphenomenal, as the correlation argument would have it (which we do not accept). Indeed, more proximal than that, it is very difficult to predict *a priori* what the behavioral outcome of damage to a given area will be or whether it would be the same or different for all the regions that were activated. If activation is related to function, as early arguments put it, why does damage to the parietal or frontal cortex not produce the severe amnesic deficits seen following damage to the MTL? Indeed, this kind of argument accounted for the early skepticism of investigators to functional neuroimaging studies when prefrontal cortex activation was so prominent; we knew from lesion studies that damage to them does not cause severe memory loss. We have learned a great deal about how to interpret functional neuroimaging data since those early days, but there is an implicit assumption that governs our interpretation, which is that our knowledge of the effects of brain damage to these regions place boundaries on our interpretation. Knowledge that damage to the lateral prefrontal cortex does not produce amnesia leads to interpretations of functional neuroimaging data that are consistent with that and other facts about the effects of frontal lesions on executive functions. The same holds for our interpretation of activations of the PPC, although in this case functions are believed to be related to other effects of parietal damage, such as those related to attention, action, and consciousness. In the same vein, there is an increasingly popular use of large network analyses to explain behavior. Findings based on these analyses need data from single-case studies, if one is to understand how damage to different nodes of the network affect behavior and, by implication, how damage to those regions affect the workings of the network. We noted some functional neuroimaging studies that combine lesion with network analyses;

yet, the number of single-case studies on which this type of very valuable analyses have been conducted can be counted on one hand.

Difficulties in translating the meaning of activations to behavior and function are even more apparent for the vmPFC. Here, too, is a structure that seems to be implicated in the acquisition and retrieval of recent and remote memories. One could never, however, have inferred from functional neuroimaging data alone that damage to this structure would lead to confabulation. Memory loss is certainly possible, but the particular form of loss seen in confabulation most likely would not have been predicted. Indeed, as noted earlier, this behavioral phenomenon initially was used to develop models of memory, such as the component process model,[205,231] but has been difficult to incorporate into more recent models of vmPFC function that are derived from functional neuroimaging data (however, see Refs. 194 and 203). Hopefully, with time, researchers will learn to interpret neuroimaging data for given brain regions so as to predict the observed losses that occur when the regions are damaged. Yet, even if possible, such interpretations would be guided by information from lesion studies in general and single-case studies in particular.

The second example is a feasibility argument. A single case can often focus an issue because of how dramatic and stark the deficit is, in a way that group studies usually cannot. The phenomenon that is revealed in a single case can then be pursued in group studies and functional neuroimaging to confirm that a comparable deficit, though likely milder, occurs in other individuals with similar damage and is, therefore, not idiosyncratic. Follow-up studies to determine the precise nature of the deficit, and the processes and mechanisms that are implicated, can be conducted much more easily in a single case of a patient who already is committed to being investigated than in a group whose many members have to be recruited and screened anew for each new study. In addition, in many single-case studies, the experimenter comes to know the individual very well, enabling him/her to appreciate the wide-ranging effects that the particular injury can have on behavior and to gain insights that can be translated into experiments and theories (e.g., see Corkin[7] for her scientific biography of H.M.).

The third point we wish to make about the value of single-case studies is a sociological and humanistic one, which is that, at bottom, we believe there is value in focusing on people and their life narratives (rather than their brain scans). It is no accident that some lectures, opening paragraphs of textbooks, and many media reports begin with a description of the behavior of a single individual. It is this focus on the individual that engages our interest in the function of a damaged brain region, more so than neuroimaging data or data from group studies—the continuing fascination with H.M. stands as a testament to this. Single-case studies stimulate interest, involvement, and sustain commitment to research and clinical applications. They engage the heart as well as the mind.

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Conflicts of interest

The authors declare no conflicts of interest.

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