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Neuropsychological Investigations of Human Amnesia: Insights Into the Role of the Medial Temporal Lobes in Cognition

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Abstract

The past 30 years of research on human amnesia has yielded important changes in our understanding of the role of the medial temporal lobes (MTL) in memory. On the one hand, this body of evidence has highlighted that not all types of memory are impaired in patients with MTL lesions. On the other hand, this research has made apparent that the role of the MTL extends beyond the domain of long-term memory, to include working memory, perception, and future thinking. In this article, we review the discoveries and controversies that have characterized this literature and that set the stage for a new conceptualization of the role of the MTL in cognition. This shift toward a more nuanced understanding of MTL function has direct relevance for a range of clinical disorders in which the MTL is implicated, potentially shaping not only theoretical understanding but also clinical practice. (*JINS*, 2017, *23*, 732–740)

Keywords: Medial temporal lobes, Hippocampus, Amnesia, Learning, Memory, Encephalitis, Hypoxia

INTRODUCTION

Since the seminal reports of H.M.'s profound memory impairment following surgical resection of the medial temporal lobes (MTL) bilaterally (Milner, Corkin, & Teuber, 1968; Scoville & Milner, 1957), detailed investigations of patients with amnesia have been invaluable in characterizing the impairment that results from MTL lesions (Squire & Wixted, 2011). MTL amnesia can result from several etiologies including ischemia, viral encephalitis, and anoxia. Over the past 30 years, much attention has been directed toward mapping the scope of impairments associated with MTL damage, and elucidating distinctions between the performance of patients with putative focal hippocampal damage and those with more extensive MTL lesions. Difficulties associated with potential hidden pathology and uncertainty about the functional status of remaining tissue notwithstanding, findings from patient studies remain an important source of information about the role of the MTL and its subregions in memory and cognition (Rosenbaum, Gilboa, & Moscovitch, 2014), and provide critical converging evidence to animal lesion studies and functional MRI. This paper provides an overview of major theoretical developments in human amnesia research over the past 30 years. These advances point to the conclusion that the scope of impairment following MTL lesions is at once *narrower* and *broader* than previously thought.

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MTL LESIONS LEAD TO SELECTIVE IMPAIRMENTS IN CONSCIOUS LONG-TERM MEMORY

The finding that H.M. and other amnesic patients performed normally on short-term memory (STM) tasks such as digit span but were severely impaired in retaining information over longer delays supported a fundamental distinction between STM and long-term memory (LTM) (Baddeley & Warrington, 1970). However, it soon became apparent that not all expressions of LTM are impaired: whereas patients with MTL lesions have poor conscious memory for events and facts (declarative memory), they show intact non-conscious learning (non-declarative memory). An early focus in non-declarative memory was on the intact acquisition of perceptuo-motor skills in amnesic patients (Milner, 1962), but subsequent studies demonstrated that patients are also able to master certain cognitive tasks through

incremental feedback-based learning, such as acquisition of an artificial grammar (Knowlton, Ramus, & Squire, 1992) or pattern classification (Knowlton, Mangels, & Squire, 1996). These forms of habit learning operate outside of awareness and are thought to involve cortico-striatal circuits. They lack the flexibility, however, associated with declarative memory (Shohamy, Myers, Kalanithi, & Gluck, 2008).

Unconscious changes in task performance due to recent experience can also be seen following a single exposure. This phenomenon, known as repetition priming, takes the form of enhanced or biased identification, generation, or classification of stimuli as a result of recent exposure to those or similar stimuli. An extensive literature has documented intact priming for pictures or words in patients with MTL lesions in tasks requiring identification of briefly flashed stimuli, completion of word stems, and verification of category membership of exemplars (Moscovitch, Vriezen, & Gottstein, 1993; Verfaellie & Keane, 2002). Notably, patients show normal repetition priming even when their recognition memory for the stimuli is at chance. Early accounts postulated that preserved priming is mediated by activation of pre-existing representations in LTM, but patients' intact priming for novel, unfamiliar stimuli (e.g., pseudowords, novel faces, or novel nonverbal stimuli) refuted this view (Verfaellie & Keane, 2001).

Another instance in which priming reflects the formation of novel representations is when the stimuli are unrelated pairs of words or images that are experimentally associated. The status of priming for novel associations in patients with MTL lesions has been of considerable interest. Whereas associative or relational processing is a hallmark of *declarative* memory, it is unclear whether *non-declarative* memory for relational representations also depends on the MTL. Some studies have shown intact priming for novel associations in amnesia, but others have not (Verfaellie & Keane, 2002). Interpretation of these results has been complicated by the fact that some instances of impaired priming in amnesia may reflect "contamination" of performance in the healthy comparison group by declarative memory. Excluding such instances, it appears that amnesic patients perform normally when priming tasks require the formation of associations within a single processing module (i.e., within-domain), but are impaired when tasks require the formation of associations across distinct processing modules (i.e., between-domain) (Verfaellie, LaRocque, & Keane, 2012). Priming is thought to reflect a general principle of neural plasticity whereby information-processing circuits are reshaped by experience (Reber, 2013). Building on this notion, we postulate that within-domain associations can be formed within closely adjacent and interacting neurons in a single processing circuit, without MTL mediation, whereas between-domain associations that are formed between distinct processing circuits depend on informational convergence within the MTL. As described below, a similar distinction between within-domain and between-domain associations has also been postulated in the context of explicit memory.

FUNCTIONAL SPECIALIZATION WITHIN THE MTL MEMORY SYSTEM

A long-held view, based on early primate lesion studies as well as human cases of amnesia that came to autopsy, has been that the hippocampus and MTL cortices (perirhinal, entorhinal, and parahippocampal cortex) form a unitary system, whereby each structure makes similar contributions to the retention of facts and events (Squire, Stark, & Clark, 2004). This view was challenged, however, by a review of human amnesia studies showing that patients with selective lesions to the hippocampus (or its diencephalic targets) had relatively preserved recognition memory in comparison to recall. Patients with more extensive MTL lesions were impaired in both types of tasks (Aggleton & Shaw, 1996). Drawing on a dual process model of recognition, Aggleton and Shaw (1996) postulated that the hippocampus is critical for recollection of contextual information but not for familiarity, whereas MTL cortical regions including perirhinal cortex mediate familiarity. This suggestion rested in part on the argument that recall performance was equivalently impaired in patients with selective hippocampal lesions and those with larger lesions, but floor effects complicate this conclusion. In subsequent years, several studies of patients with putative focal hippocampal lesions demonstrated selective impairments in recollection, but other studies observed impairments both in recollection and in familiarity (reviewed in Eichenbaum, Yonelinas, & Ranganath, 2007). Reasons for these discrepant results are unclear, although they have sometimes been ascribed to differences in lesion extent. Another criticism has been that comparisons of recollection and familiarity are confounded by memory strength, and that selective impairment in recollection following focal hippocampal damage may simply reflect inability to retrieve strong and detailed memories. By this view, hippocampal damage leaves intact a weaker form of memory that can be mediated by perirhinal cortex (Wixted & Squire, 2011). Compelling evidence against this argument, however, comes from a patient who, as treatment for intractable epilepsy, underwent a rare resection of the left anterior temporal lobe, which included large aspects of perirhinal and entorhinal cortex as well as amygdala[1]. This patient showed impaired familiarity but intact recollection (Bowles et al., 2007). Importantly, the selective impairment in familiarity was observed at the same level of memory strength at which other patients showed selective recollection deficits (Bowles et al., 2010).

Recollection is by nature relational, in that it enables the reactivation of contextual elements associated with an item. As such, this framework fits within the larger view that proposes that the primary role of the hippocampus is to bind together the constituent elements representing an event (Cohen & Eichenbaum, 1993). Consistent with the role of the

[1] There was also mild atrophy of the left hippocampus, although not nearly as pronounced as that observed in extrahippocampal cortices. Furthermore, the hippocampal atrophy predated the surgery, and in the context of long-standing epilepsy, its functional significance is unclear.

hippocampus in such relational processing, amnesic patients perform poorly on associative recognition tasks even when their item recognition is equated to that of control subjects (Giovanello, Verfaellie, & Keane, 2003; Kan, Giovanello, Schnyer, Makris, & Verfaellie, 2007).

Yet, the extent to which associative memory is hippocampally dependent appears to vary. For instance, when stimuli can be unitized at encoding, as when two unrelated words are encoded as a novel compound with a specific meaning, performance can be supported in part by familiarity, and patients with hippocampal damage show some degree of sparing of associative recognition (Quamme, Yonelinas, & Norman, 2007). Further illustrating that not all associative memories have the same functional or neural basis, two studies of patients with selective hippocampal damage observed impaired recognition of between-domain associations but intact recognition of within-domain associations (Mayes et al., 2004; Vargha-Khadem et al., 1997). These findings led Mayes, Montaldi, and Migo (2007) to propose that whereas informational elements that make up within-domain associations converge in MTL cortical structures that mediate familiarity, elements that make up between-domain associations depend on the hippocampus, where stimuli processed in distinct cortical regions converge. Subsequent evidence in support of this domain-dichotomy view, however, has been mixed (for discussion, see Borders, Aly, Parks, & Yonelinas, 2017).

The notion that the hippocampus binds different types of information fits well with the anatomical evidence that places the hippocampus at the top of the MTL processing hierarchy. Elaborating this view and focusing specifically on the binding of item and contextual information, a further division of labor within the MTL has been suggested whereby the hippocampus receives input from perirhinal cortex about specific items and input from parahippocampal cortex about contextual information (Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007). Evidence in support of the latter has come primarily from functional imaging studies, but this view also receives support from the finding that patients with right parahippocampal lesions have spatial memory deficits (Bohbot et al., 1998).

Notably, it has been postulated that recollection and familiarity are associated with distinct forgetting mechanisms, namely decay and interference, respectively (Sadeh, Ozubko, & Moscovitch, 2014). Hippocampally mediated binding of item and context information allows for the creation of distinct representations of overlapping memories (pattern separation). As such, hippocampal representations are less vulnerable to interference, with forgetting primarily resulting from decay. By contrast, familiarity-based memories mediated by perirhinal cortex do not enjoy the protection from interference afforded by pattern separation and thus are more sensitive to interference than to decay. This dichotomy could explain why patients with hippocampal lesions are particularly sensitive to the effects of interference (Dewar, Della Sala, Beschin, & Cowan, 2010), but more research is needed to directly test these ideas.

REMOTE MEMORY DEFICITS IN MTL AMNESIA AS A WINDOW ON MEMORY CONSOLIDATION AND TRANSFORMATION

Early descriptions of retrograde amnesia indicated that amnesic patients have better recall for premorbid memories from the remote past than from the time period closer to the onset of amnesia. This pattern gave rise to the view that MTL structures make a temporary contribution to declarative memory. Known as standard consolidation theory, this view states that the MTL, and in particular the hippocampus, interacts with distributed neocortical regions to support the initial formation of a memory, but through a gradual process of consolidation over time, these same memories can be retrieved neocortically, without hippocampal mediation (Squire & Alvarez, 1995). This consolidation view assumes a similar process of reorganization for memories of specific events (episodic memories) and knowledge of facts or nonpersonal information (semantic memories).

Subsequent re-evaluation of the evidence, however, suggested that these two forms of memory can be affected differentially by hippocampal damage. Whereas semantic memories are relatively preserved, the loss of episodic memory may extend for decades (Nadel & Moscovitch, 1997). This evidence gave rise to multiple trace theory (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). By this theory, the hippocampus binds together informational elements processed in distinct neocortical regions; each time a memory is reactivated, a novel hippocampal trace is created that reinforces the episodic memory. The retrieval of details unique to specific events is thought to remain hippocampally dependent, regardless of the age of the memory. The extent to which detailed episodic memories are affected by hippocampal damage depends on the frequency of their retrieval and reactivation. At the same time, the neocortex extracts the regularities across different episodes, resulting in abstraction of semantic memories that can be retrieved without hippocampal involvement.

Elaborating on this view, it has been suggested that episodic memories can be qualitatively transformed over time from detailed contextual memories to schematic, gist-like memories that are devoid of specific details. These transformed memories, like semantic memories, are not affected by hippocampal damage (Winocur, Moscovitch, & Bontempi, 2010).

Studies evaluating the timescale of hippocampal involvement in remote episodic memory have produced conflicting results. One difficulty with this literature is that many studies purporting to support consolidation theory (reviewed in Lah & Miller, 2008) have not probed memories in such a way as to capture the contextual richness associated with episodic reliving. More recently, a protocol that allows for the quantification of episodic details (pertaining to the temporal, spatial or perceptual features of the event) in memory narratives has been used as a sensitive measure of episodic recollection (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002).

Using this protocol, Rosenbaum and colleagues (Rosenbaum et al., 2008) found that, in a sample of four patients, the ability to retrieve episodic details was inversely linked to the extent of hippocampal damage. In another study, the narratives of patients with MTL lesions, including a patient with focal hippocampal lesion, were significantly impoverished when they recounted memories from the distant past, even though consolidation of such events should have been completed before onset of amnesia (Race, Keane, & Verfaellie, 2011).

Both of these findings are consistent with multiple trace theory. However, using a similar approach, another study found that recollection of episodic details pertaining to events from childhood through middle age was intact following hippocampal lesions (Kirwan, Bayley, Galvan, & Squire, 2008). Thus, the neuropsychological literature remains divided. Although several factors have been proposed to explain the conflicting findings, there is at present no clear resolution to this debate (Dede & Smith, 2016; Winocur et al., 2010). The potential impact of different approaches to testing and scoring autobiographical memory also has garnered recent attention and remains an area of active investigation (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Rensen et al., 2017).

HIPPOCAMPAL LESIONS IMPAIR NOT ONLY LTM BUT ALSO STM

Motivated by the notion that hippocampal lesions impair LTM by disrupting the encoding and retrieval of *relational* information, recent studies have explored whether hippocampal lesions may also lead to impairments in STM tasks that pose relational demands. Such indeed appears to be the case. For instance, in one study (Olson, Page, Moore, Chatterjee, & Verfaellie, 2006), patients with hippocampal lesions were sequentially presented with three objects in three distinct locations, and after a 1- or 8-s. delay were tested on their recognition memory for objects, locations, or object-location pairings. Patients performed normally in the object and location conditions, but were impaired in recognizing object-location pairs, even at a delay of 1 s.

Similarly, Hanula, Tranel, and Cohen (2006) showed that anoxic patients with MTL lesions had poor recognition memory for the relations among items in a scene as well as for face-scene pairings, even when the study and test image immediately followed one another. Consistent with the notion that these impairments are related to the requirement to link different elements of information together, when asked to recall the location of items, patients often mislocalize objects to the locations of other to-be-remembered objects (Pertzov et al., 2013; Watson, Voss, Warren, Tranel, & Cohen, 2013). Notably, impairments in STM are not limited to tasks that involve spatial information, but extend to associations between items, between items and colors, and temporal sequences (Graham, Barense, & Lee, 2010; Yonelinas, 2013). Impairments in STM for faces have also been observed, a finding similarly thought to reflect the high demands on relational processing.

Tasks that assess relational memory are often more difficult than those that assess memory for individual features, and thus are more likely to exceed STM demands. As such, it has been argued that the impairment in amnesia reflects an inability to recruit LTM to support performance in a nominally STM task rather than a STM deficit *per se*. Consistent with this notion, several studies have found impairments in amnesia in STM performance only when the memory load is high or the retention interval is extended (Jeneson & Squire, 2012). Although such an explanation cannot account for all findings (e.g., Race, LaRocque, Keane, & Verfaellie, 2013), intact performance under low STM load conditions highlights that hippocampal lesions do not always disrupt performance on relational STM tasks.

Attempting to reconcile these discrepant findings, Yonelinas (2013) has proposed that the hippocampus is involved in STM binding specifically when a task requires fine-grained ("high resolution") discrimination. In a direct test of this proposal, Koen and colleagues (Koen, Borders, Petzold, & Yonelinas, 2016) compared the performance of MTL patients in visual STM tasks that required high-resolution binding (e.g., remembering an item's exact shade of red) and low-resolution binding (e.g., remembering whether an item was red or blue); these tasks were matched in difficulty by adjusting the memory load. Consistent with their proposal, Koen et al. (2016) found that MTL patients were impaired in visual STM for high-resolution bindings but not for low-resolution bindings. Although further work is needed to test this hypothesis, it has become clear that memory impairments following hippocampal lesions do not honor the traditional distinction between STM and LTM, but rather can be understood with reference to the role of the hippocampus in forming relational representations.

BEYOND MEMORY: VISUAL PERCEPTION FOLLOWING MTL LESIONS

Further extending the scope of MTL involvement beyond memory, a body of research now suggests that MTL lesions can also be associated with perceptual deficits (Graham et al., 2010; Lee, Yeung, & Barense, 2012). Motivated by findings in nonhuman primates suggesting that perirhinal cortex is situated at the apex of the ventral visual processing stream, Lee, Bussey, et al. (2005) tested MTL patients on a visual discrimination task consisting of stimuli that were blended to create different levels of featural overlap. Patients with MTL lesions encompassing perirhinal cortex were impaired when objects, faces, or scenes contained high feature overlap. These same patients also performed poorly on an oddity task requiring identification of the odd stimulus among a set of novel objects or faces presented from different viewpoints (Lee, Buckley, et al., 2005). However, when performance could be based on simple features, such as color or shape, or when all stimuli were presented from the same viewpoint,

no impairments were observed, suggesting that perirhinal lesions do not cause a general perceptual deficit. In patients with lesions limited to the hippocampus, a different pattern of performance was seen. These patients performed well when the stimuli were faces or objects, but had difficulty performing discrimination or oddity tasks involving scenes (Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005).

Arguably, even such perceptual tasks pose demands on STM memory, insofar as they require keeping information in mind while making perceptual comparisons. Thus, such findings leave open the possibility that the function of perirhinal cortex is limited to memory and does not extend to perception. Consistent with this notion, there is evidence that when STM demands are minimized, patients with MTL lesions perform normally (Knutson, Hopkins, & Squire, 2012, 2013). On the other hand, impairments have been observed on perceptual tasks that pose no obvious STM demands, such as tasks requiring judgments of structural integrity (Lee & Rudebeck, 2010) or figure-ground assignment (Barense, Ngo, Hung, & Peterson, 2012).

Such findings provide support for an alternative view that does not limit the role of the MTL to memory, but instead posits that regions within the MTL are specialized for the creation of distinct kinds of conjunctive representations – representations that can be used in the service of both perception and memory. This view postulates a functional segregation within the MTL, with perirhinal cortex representing relations among features within objects, and the hippocampus, possibly in combination with parahippocampal cortex, representing complex spatial configurations among objects. By this view, MTL patients' normal performance on some visual discrimination tasks is attributed to the fact that those tasks insufficiently tax conjunctive processing (Lee et al., 2012). What is needed to resolve this debate is a way to assess, independently from performance in amnesia, the contribution of memorial or relational processes to task performance.

IMAGINING THE FUTURE IN MTL AMNESIA

In the past decade, memory researchers have been interested in episodic memory not only for its role in remembering the past, but also for its role in imagining possible future events. Correspondingly, there has been a strong interest in the consequences of amnesia for envisioning the future and engaging in other forms of future-oriented cognition. Amnesic patients' inability to conceive of their own future was described initially in case studies of patients with diffuse lesions (reviewed in Verfaellie, Race, & Keane, 2012), but the first study to link impairments in imagining new experiences specifically to MTL lesions came from Hassabis and colleagues (Hassabis, Kumaran, Vann, & Maguire, 2007).

When asked to construct imagined scenarios, such as "lying on a white sandy beach in a tropical bay," patients gave descriptions that were impoverished in content and lacked spatial coherence. Another study directly compared MTL patients' ability to recall personal events from the past and to construct personal events in the future (Race et al., 2011). Patients provided fewer episodic details in both the past and future conditions, a finding that was not due to a more basic difficulty with narrative construction. Furthermore, the number of episodic details for past and future narratives was correlated, suggesting that a common MTL mechanism underlies memory and future thinking. The close link between memory and future thinking may explain why, in a group of MTL patients who did not show impairments in premorbid episodic memory, future thinking was intact as well (Squire et al., 2010).

Imagining a novel event involves two main components: the retrieval of episodic details from memories of experienced events that function as the building blocks for an imagined scenario, and the flexible recombination of these elements in a novel way to construct a coherent simulation (Schacter, Addis, & Buckner, 2007). Amnesic patients have difficulty accessing episodic details from past events, but it is unknown whether this impairment in itself fully accounts for their future thinking impairment. Romero and Moscovitch (2012) addressed this question by making the elements that form the core of an event or scene (the objects and the setting) available to MTL patients and asking them to create a novel event by relating the various elements to one another in the provided context. MTL patients made fewer inter-item relations than did controls, and this impairment grew more pronounced with an increase in the number of elements to be incorporated. These findings suggest that the impairment is not simply due to an inability to retrieve details, but also reflects a deficit in recombining those details into a coherent event.

These results are also consistent with an alternative view that posits that the fundamental deficit following MTL lesions is an inability to construct spatially coherent scenes (Hassabis et al., 2007). Interestingly, an inability to combine information in novel ways may have even more far-reaching consequences, as MTL lesions also lead to impairments in creative thinking (Duff, Kurczek, Rubin, Cohen, & Tranel, 2013) and open-ended problem solving (Sheldon, McAndrews, & Moscovitch, 2011).

The ability to imagine future events and outcomes confers adaptive value in allowing us to pre-experience the consequences of our choices before making decisions. Thus, one might expect future-thinking deficits to have functional consequences for future-oriented decisions. This is indeed the case. Considerable evidence shows that the tendency to engage in temporal discounting (i.e., to choose a smaller present reward over a larger future reward) is attenuated in cognitively intact individuals when they imagine consuming the reward in the context of a future event. This attenuation is absent in patients with MTL lesions (Palombo, Keane, & Verfaellie, 2015). Interestingly, patients can show the expected attenuation when prompted to think about the future in semantic terms, using factual information and reasoning (Palombo, Keane, & Verfaellie, 2016). To what extent such semantic future thinking can support patients' decision

making in everyday life is an important question for future research.

FUTURE DIRECTIONS IN AMNESIA RESEARCH

With the advent of brain connectivity research, there has been growing awareness of the potential impact of focal lesions on regions distant from the lesion location. The implications of such connectivity changes for understanding MTL amnesia remain to be elucidated. The MTL forms part of an extensive intrinsic functional network known as the default mode network, which also comprises the posterior cingulate, lateral parietal regions, and medial prefrontal regions. Initial evidence suggests that MTL lesions impact the default network broadly, not only by virtue of altered functional connections to and from the hippocampus, but also through within-network alterations between areas distal to the hippocampus (Hayes, Salat, & Verfaellie, 2012; Henson et al., 2016) and disrupted connectivity between networks (Henson et al., 2016).

Aside from its connectivity with other cortical regions, the MTL also has strong connectivity, both structurally and functionally, with the diencephalon as part of the Papez circuit. Injury to the MTL has functional implications for the diencephalon (Reed et al., 1999), and similarly, injury to the diencephalon has functional implications for the MTL and default mode network more broadly (Jones, Mateen, Lucchinetti, Jack, & Welker, 2011; Reed et al., 2003). Yet, how each of these structures contributes to memory remains to be elucidated. Although this review has focused on the role of the MTL in memory, an equally important question is whether diencephalic structures are subservient to the MTL or contribute themselves in critical ways to memory.

How changes at a network level map onto cognitive changes, in memory and beyond, provides fertile ground for future study. Conceivably, different patterns of connectivity change across patients with focal MTL lesions may be associated with distinct cognitive outcomes. Thus, such studies have the potential to reconcile discrepant findings in the literature that until now appeared intractable.

A focus on functional networks rather than on the MTL in isolation does not diminish the importance of studying patients with focal lesions. To the contrary, by directly comparing the effects of lesions to distinct nodes in the network, we stand to gain new understanding about their distinct functional roles. For instance, within the domain of LTM, evidence suggests that not only hippocampal lesions, but also lateral parietal lesions are associated with abnormalities in recollection (Ben-Zvi, Soroker, & Levy, 2015; Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007). Similarly, impairments in future thinking are not unique to patients with MTL lesions, but have also been described in patients with ventromedial prefrontal lesions (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016). A direct comparison of the performance of distinct focal lesion groups on tasks with well-specified cognitive demands may yield further insight into how each of these regions participates in a larger functional network and contributes distinct component processes. At the same time, better specification of hippocampal lesions, whether with regard to affected hippocampal subfields or anterior/posterior extent, will be critical to aligning human findings with computational mechanisms postulated on the basis of neuroimaging studies and lesion studies in animals.

Paradoxically, by elucidating the scope of the impairment associated with MTL lesions, neuropsychological studies of amnesia have simultaneously sharpened distinctions between discrete forms of memory and blurred distinctions between episodic memory and other cognitive functions. With regard to the distinction between non-declarative and declarative memory, an important task for future research is to examine how these forms of memory interact. For instance, we recently demonstrated that MTL patients perform normally on a feedback-based probabilistic learning task when feedback is provided immediately, but not when feedback is delayed by 7 s, suggesting that under delayed conditions hippocampal mechanisms influence learning that is typically striatally mediated (Foerde, Race, Verfaellie, & Shohamy, 2013). Understanding the nature of such impairment not only will illuminate the interdependency of neural systems but may also help pinpoint specific mechanisms by which the hippocampus and other MTL sub-regions contribute to performance.

More broadly, regarding the link between memory and other cognitive functions, an outstanding question is how mnemonic processes are leveraged in the service of other aspects of cognition. Shohamy and Turk-Browne (2013) have outlined two possibilities. One is that basic computational mechanisms subserved by the hippocampus or other MTL regions are shared among cognitive domains. Illustrating such a view, Yonelinas (2013) suggested that the process distinction between recollection and familiarity that has shaped understanding of recognition memory and its neural bases, may also be usefully applied to perception. An important contribution of neuropsychological studies to this inquiry will be to assess such component processes across domains in the same patients. Alternatively, memorial representations may modulate the operation of other processing systems that do not themselves require MTL mediation. For example, performance on a standard temporal discounting paradigm does not depend on the MTL but as discussed above, future thinking, which depends on the retrieval and recombination of memorial information, can attenuate discounting in this paradigm (Palombo et al., 2015). The study of amnesic patients provides a unique way to assess a range of behaviors in the absence of memorial influence, and by inference, to inform how behavior is normally shaped by prior experience.

That MTL lesions can interfere with performance in domains other than memory is not meant to obscure the clinical reality that declarative memory problems are the primary, and typically unique, presenting problem. Indeed, to

what extent (and under what circumstances) impairments in other cognitive domains highlighted here impact functioning in naturalistic settings remains to be elucidated. Yet, the study of patients with MTL amnesia serves as a model system for understanding impairments in other disorders that affect the MTL, such as aging and dementia. Notably, identification of extra-memorial impairments in the laboratory has already informed clinical assessment. For instance, it has been shown that STM binding is impaired in Alzheimer's disease but not in other dementias (Della Sala, Parra, Fabi, Luzzi, & Abrahams, 2012; Lee, Rahman, Hodges, Sahakian, & Graham, 2003) and is a sensitive marker of preclinical Alzheimer's disease (Blackwell et al., 2004). We anticipate that neuropsychological studies of amnesia will continue to form a central nexus between theoretical insight and clinical practice.

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