HIPPOCAMPUS 22:1577–1588 (2012)

Hiding in Plain View: Lesions of the Medial Temporal Lobe Impair Online Representation

David E. Warren,[1*] Melissa C. Duff,[1,2] Unni Jensen,[3] Daniel Tranel,[1] and Neal J. Cohen[4,5]

ABSTRACT: The hippocampus is necessary for the normal formation of enduring declarative memories, but its role in cognitive processes spanning short intervals is less well understood. Within the last decade, several reports have described modest behavioral deficits in medial temporal lobe (MTL)-lesion patients when they perform tasks that do not seem likely to rely on enduring memory. An intriguing but sparsely-tested implication of such results is that the MTL is involved in the online representation of information, possibly of an associative/relational nature, irrespective of delay. We administered several tests that simultaneously presented all information necessary for accurate responses to a group of MTL-lesion patients with severe declarative memory deficits but otherwise normal cognition, and to matched brain-damaged and healthy comparison participants. MTL-lesion patients performed less well than either comparison group in the Hooper Visual Organization Test, and several patients performed outside the normal range on the Overlapping Figures Test. A novel follow-up borrowing characteristics of the Overlapping Figures Test revealed impaired identification of novel items by MTL-lesion patients when target items were obscured by distracters, and two additional novel tests of fragmented object identification further implicated the hippocampus/MTL in the integration of information across very brief intervals. These findings suggest that MTL structures including the hippocampus contribute similarly to cognition irrespective of timescale. © **2011 Wiley Periodicals, Inc.**

KEY WORDS: memory; STM; WM; MTL; hippocampus; amnesia

INTRODUCTION

The hippocampus is known to be necessary for the normal formation of declarative memories (Scoville and Milner, 1957; Cohen and Squire, 1980), and appears to play a special role in the binding together of arbitrarily-related representations (Eichenbaum and Cohen, 2001; Davachi and Dobbins, 2008; Ranganath, 2010). According to one prominent theory, this binding operation is always ongoing, occurring automatically and obligatorily, yielding flexibly-accessible, enduring memories that can be cued by any component representation (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001). This encompasses the longstanding association between the hippocampus and psychology's theoretical construct of long-term memory, but the continuous binding operations performed by the hippocampus are not necessarily contained within that construct's boundaries. In the investigation presented here, we aimed to study the functions of the hippocampus by administering tasks which presented all of the information necessary for accurate performance to patients with bilateral hippocampal damage, but our design goal was orthogonal to issues of what constitutes long-term or working memory. Rather, we pursued a more thorough understanding of hippocampal function irrespective of timescale by studying the influence of the hippocampus within very short intervals.

Experimental and anecdotal evidence regarding hippocampal influence across short durations has been mixed. During the first decades in which the cognitive neuroscience of memory was studied, results seemed to indicate that the hippocampus did not participate in cognition within brief intervals. Relevant experiments tested patients with hippocampal lesions using stimuli ranging across spans of single digits, cued spatial recall (Drachman and Arbit, 1966), three-digit numbers, pure tones (Wickelgren, 1968), spatial memory (Warrington and Baddeley, 1974), word lists (Baddeley and Warrington, 1970), consonant trigrams (Sidman et al., 1968), dot arrays, angles, and mirror-reversed objects (Cave and Squire, 1992) among many others. Almost universally, patients performed as well as healthy comparisons, leading to conclusions that hippocampal function was closely tied to the construct of long-term memory.

However, work reported more recently has suggested that hippocampal contributions may influence ongoing cognition or online processing within similarly short periods of time. Hannula et al., 2006

[1] **Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, University of Iowa College of Medicine, 200 Hawkins Dr, Iowa City, Iowa;** [2] **Department of Communication Sciences and Disorders, The University of Iowa, Iowa City, Iowa;** [3] **NIH/National Institute for Neurological Disorders and Stroke, Bethesda, Maryland;** [4] **Department of Psychology, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, Illinois;** [5] **Department of Neuroscience, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, Illinois**

Grant sponsor: NINDS; Grant number: P01 NS19632; Grant sponsor: NIMH; Grant number: RO1 MH062500.

*Correspondence to: David E. Warren, Department of Neurology, University of Iowa College of Medicine, 200 Hawkins Dr, 2192 RCP, Iowa City, Iowa 52242, USA. E-mail: davideugenewarren@gmail.com

Accepted for publication 3 November 2011
DOI 10.1002/hipo.21000
Published online 19 December 2011 in Wiley Online Library (wileyonlinelibrary.com).

TABLE 1.

MTL-lesion Patients

							WAIS			WMS
Patient ID	Etiology	Sex	Hand	Onset	Age (2008)	Ed.	VIQ	MR	Vcb.	GMI
1846	Anoxia	F	R	1993	45	14	89	10	8	57
1951	HSE	M	R	1980	56	16	105	13	10	57
2308	HSE	M	L	1999	52	16	95	12	11	45
2363	Anoxia	M	R	1998	52	16	112	11	12	73
2563	Anoxia	M	L	2000	53	16	91	9	9	63

Demographic and neuropsychological characteristics of the MTL-lesion patient group.
WAIS, Wechsler adult intelligence scale-III; VIQ, verbal IQ; MR, matrix reasoning subtest; Vcb., vocabulary subtest; WMS, Wechsler memory scale-III; GMI, general memory index; HSE, herpes simplex encephalitis; DRI, delayed recall index. For the WMS-III, the DRI is an average of the auditory delayed index and visual delayed index.

tested patients with focal hippocampal lesions in two different relational-memory tasks involving study episodes followed by tests after some further number of studied items had intervened. Even when only seconds had elapsed since study and in the absence of any intervening items, patients possessed impoverished relational knowledge of items in scenes, and likewise relational knowledge of face-scene pairings was deficient. Similarly, Cashdollar et al. (2009) noted impaired scene recognition by patients with bilateral hippocampal sclerosis when tested in a configural-relational condition that required spatial relations within scene stimuli to be maintained for 5 s. Olson et al. (2006) also investigated relational memory after short delays in a pair of experiments using sequential presentation of spatially distributed items. Lesion patients' relational memory performance was impaired relative to healthy comparisons after both 1 s and 8 s delays from the study epoch. Finally, Ryan and Cohen (2004) noted that the eye movements of amnesic patients to scene stimuli were reliably different than those of healthy participants even when the delay between study and test was very brief, approximately 1 s (but see Baddeley et al., 2010).

These findings suggest that relational representation may depend on the hippocampus even across intervals on the order of seconds. Importantly, relational memory theory (Eichenbaum et al., 1992; Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001) posits that hippocampal-dependent relational representation serves not only as a means of preserving knowledge in a distributed fashion across the cortex, but more specifically as a process permitting integration and comparison of discrete experiences or items. Given that the influence of hippocampal contributions is evident over very short intervals, it could be inferred that disruption of normal hippocampal function might be revealed by changes in performance of tasks that would benefit from relational representation irrespective of whether those tasks require any active maintenance.

We hypothesized that hippocampus-dependent relational representations affect cognition even when no apparent memory load is imposed. If this is true, MTL-lesion patients tested with materials that do not benefit from relational representation should perform normally, but when the same patients perform a task that would benefit from relational representation, their performance should be deficient relative to healthy comparison participants. Even existing neuropsychological tests that do not explicitly impose delays may still tax relational representation if the materials are sufficiently complex and require multiple comparisons. Impaired performance of such tasks by MTL-lesion patients would support the hypothesis that the MTL contributes to relational representations in a continuous and ongoing fashion.

In order to test this, a well-characterized group of severely amnesic patients with MTL lesions were tested using two standard neuropsychological instruments and three novel experiments. Importantly, the cognitive deficits of the participating patients were principally limited to long-term declarative memory; if this was not the case, deficits observed in the current study could not be unambiguously tied to hippocampal damage (see Table 1). None of our tests explicitly depended on long-term memory, but each required that information be compared and integrated for successful performance, and might have therefore benefited from relational representation. If the hippocampus supports relational representation irrespective of delay, then we would expect to see less-than normal performance in patients with hippocampal damage. Furthermore, previous reports have implicated the hippocampus in online relational representation with greater (Hannula et al. 2006) or lesser (Olson et al., 2006) anatomical specificity, but our sample included patients with both focal hippocampal lesions and more extensive MTL lesions, and differences between the two groups would potentially be diagnostic in this matter.

Earlier investigations studying relational memory problems in MTL-lesion patients after short intervals have failed to address whether these deficits are selectively related to those MTL lesions. MTL-lesion patients' deficit in relational memory after short delays is typically less robust than the stark contrasts between normal and amnesic memory after long delays, and it is possible that these relatively small differences could be due to stereotypic cognitive changes associated with brain injury. Even after an acute phase during which defective cognition typically improves, brain injuries are typically associated with a variety of generic changes in cognition that result in slowed response times and increased susceptibility to fatigue. Our work accounts for

TABLE 2.

Brain-Damaged Comparison Participants

Patient ID	Etiology	Sex	Hand	Onset	Age (2010)	Ed.	WAIS VIQ	WAIS MR	WAIS Vcb.	Exp.
0297	L Fr. ACoA An.	M	R	1981	61	16	112	8	13	1AB, 2AB, 3AB
1290	L Tmp. Hem.	F	R	1982	54	15	108	14	14	1A, 3AB
1652	L Fr. ACoA An.	M	R	1991	55	11	95[a]	7*	8*	1AB, 2B, 3AB
1656	R Tmp. Inf.	M	R	1992	67	12	101	9	12	1A, 3A
1815	B Fr. MR	M	R	1997	60	20	121	11	13	1A, 3AB
2710	L Par. Hem.	M	R	2000	73	16	112	15	13	1A, 2B
3001	R Fr. MR	M	R	2002	66	14	100[a]	13[a]	12[a]	1A, 3AB
3093	L Fr./BG Inf.	M	R	2002	55	16	89	9	5	1AB, 2AB, 3AB
3137	L Fr. AVM Em.	M	R	2003	58	16	107	12	12	1AB, 2AB, 3AB
3138	L MCA Inf.	F	R	2004	56	12	78	9	7	1A, 2B
3223	R BG Hem.	M	R	2005	46	16	113	13	15	1AB, 2AB, 3AB
3319	R Fr./Par. MR	F	R	2005	57	14	85	12	9	1AB, 2AB, 3AB
3579	L Occ. Inf.	F	R	2009	53	12	83	8	7	1A, 3A

Demographic and neuropsychological characteristics of our BDC group. Fr., Frontal; Tmp., Temporal; Occ., Occipital, BG, Basal Ganglia; ACoA, anterior communicating artery; MCA, middle cerebral artery; An., aneurysm; Em., Embolization; MR, Menigioma resection; Inf., Infarct; Hem., Hemorrhage (see Table 1 for more abbreviations).

[a]Indicates patients who completed the WAIS-IV rather than the WAIS-III.

this by including both healthy normal comparison (NC) and brain-damaged comparison (BDC) participants.

METHODS

Participants

Five MTL-lesion participants (MTL patients) completed each experiment in this report (1846, 1951, 2308, 2363, 2563). For Experiments 2A, 2B, 3A, and 3B, five healthy NC participants were each matched pairwise to the MTL patients on sex, age, handedness, and education. For Experiment 1, a different group including five pairs of NC participants was matched to the five participating MTL patients by sex, handedness, age, and education. A minimum of five BDC participants completed each experiment as well. All participants granted informed consent before beginning each experiment.

All participating MTL and BDC patients were recruited from the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience at the University of Iowa and have been thoroughly characterized neuropsychologically (see Tables 1 and 2). Each MTL patient exhibits a gross impairment in declarative memory function and relatively spared cognitive abilities according to many standard tests. The MTL and BDC groups were statistically similar on demographic and non-mnemonic neuropsychological variables: mean group ages were 51.600 (sd = 4.037) and 58.538 (sd = 6.995) years ($T(16) = 2.065$, $P = 0.056$); mean years of education were 16.400 (sd =1.673) and 14.615 (sd = 2.468) ($T(16) = 1.478$, $P = 0.159$); mean WAIS III/IV verbal IQ scores were 98.400 (sd = 9.788) and 100.308 (sd = 13.400) ($T(16) = 0.288$, $P = 0.777$); mean matrix-reasoning subtest scores were 11.000 (sd = 1.581) and 10.769 (sd = 2.587) ($T(16) = 0.185$, P = 0.856); and mean vocabulary subtest scores were 10.000 (sd = 1.581) and 10.769 (sd = 3.166) ($T(16) = 0.512$, $P = 0.615$). Additionally, all patients performed well on extensive tests of object naming across several domains (Damasio et al., 2004); mean percent correct naming across the domains of tools and animals was 94.720% (sd = 1.071%) for MTL patients and 96.604% (sd = 2.010%) for the BDC participants. Whole-brain structural scans of MTL patients who were eligible for MRI exam revealed focal hippocampal damage in some cases (1846, 2363), and extensive lesions including the temporal and medial temporal lobes in others (2308, 1951) (Allen et al., 2006; Feinstein et al., 2009). Visual inspection of CT scans for the remaining patient (2563) indicated focal hippocampal damage. Structural MRI or CT scans of BDCs were visually inspected to ensure that no MTL damage was evident.

Equipment

The computerized tasks of Experiments 2B, 3A, and 3B were administered using Presentation software (Neurobehavioral Systems, Inc.). Stimuli were presented on a 53-cm LCD monitor (NEC), and participants were seated at a comfortable viewing distance of approximately 90 cm. Button-press responses were collected with a PS/2 keyboard.

Analysis

Data aggregation was accomplished with Python software (2.6), and all analyses were conducted in R software (2.12.0). *T*-tests reported for experimental tasks were conducted without the

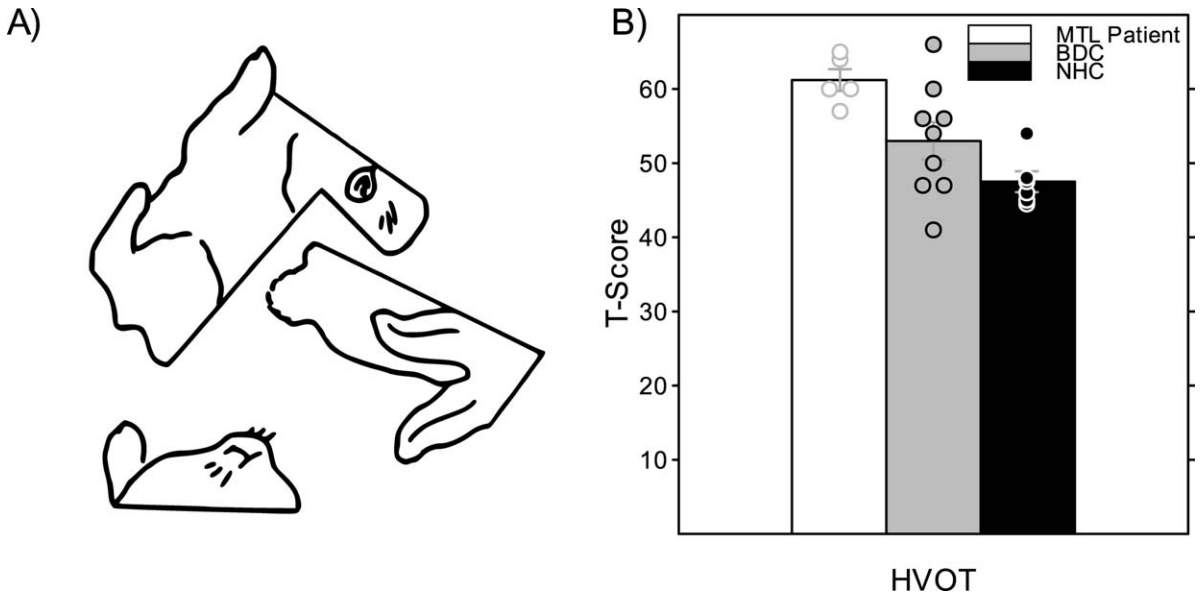

FIGURE 1. Materials and results from Experiment 1. A: Sample stimulus (Item 24) from Hooper Visual Organization Test (Hooper, 1958) reprinted by permission of the copyright holder. The HVOT requires participants to identify 30 scrambled objects similar to the sample. B: Group mean (bars) and individual (points) performance on the HVOT. Whiskers indicate ± 1 s.e.m.

assumption of equal variance distributions and therefore use the Welch–Satterthwaite approximation for degrees of freedom.

EXPERIMENT 1

Participants

MTL and NC participants were as above, and 9 BDCs also completed the task (see Table 2).

Materials

The materials for the Hooper Visual Organization Test (HVOT, Hooper, 1958) were obtained and employed (see Fig. 1A). Each test item consisted of single line drawing of a familiar object which had been divided into pieces that had been rotated and spatially scrambled.

Task

The HVOT was administered to each participant group according to the provided instructions (Hooper, 1958). Participants were asked to identify the object depicted in the scrambled line drawing.

Results

Performance on the HVOT was evaluated between participant groups using *T*-scores derived from raw performance data (see Fig. 1B). Data from the five pairs of NCs were collapsed into five summary scores in order to match the number of MTL patients. Group-level differences were evaluated using an ANOVA ($F(2,17) = 7.743$, $P < 0.005$). Planned comparisons were conducted between groups: MTL patients performed reliably less well than both NCs ($T(8.813) = 6.733$, $P < 0.001$) and BDCs ($T(11.637) = 2.803$, $P < 0.05$); the difference between NCs and BDCs was marginal ($T(11.637) = 1.896$, $P = 0.083$).

Discussion

Unusual impairments were evident in HVOT recognition performance for the MTL patients even relative to BDCs.

EXPERIMENT 2A

Participants

MTL and NC participants were as above, and 5 BDCs also completed the task (see Table 2).

Materials

This experiment used the Overlapping Figures Test (Della Sala et al., 1995), a well-characterized neuropsychological test that included two types of stimulus materials in separate trials, either common objects or novel figures. Each test item was composed of a jumble of overlapping items composed of 3–5 objects presented along with 10 response alternatives. All test trials were administered using paper copies of the original materials (see Fig. 2A).

Task

Details about administration procedures, stimuli, and scoring are available in the originating report (Della Sala et al., 1995).

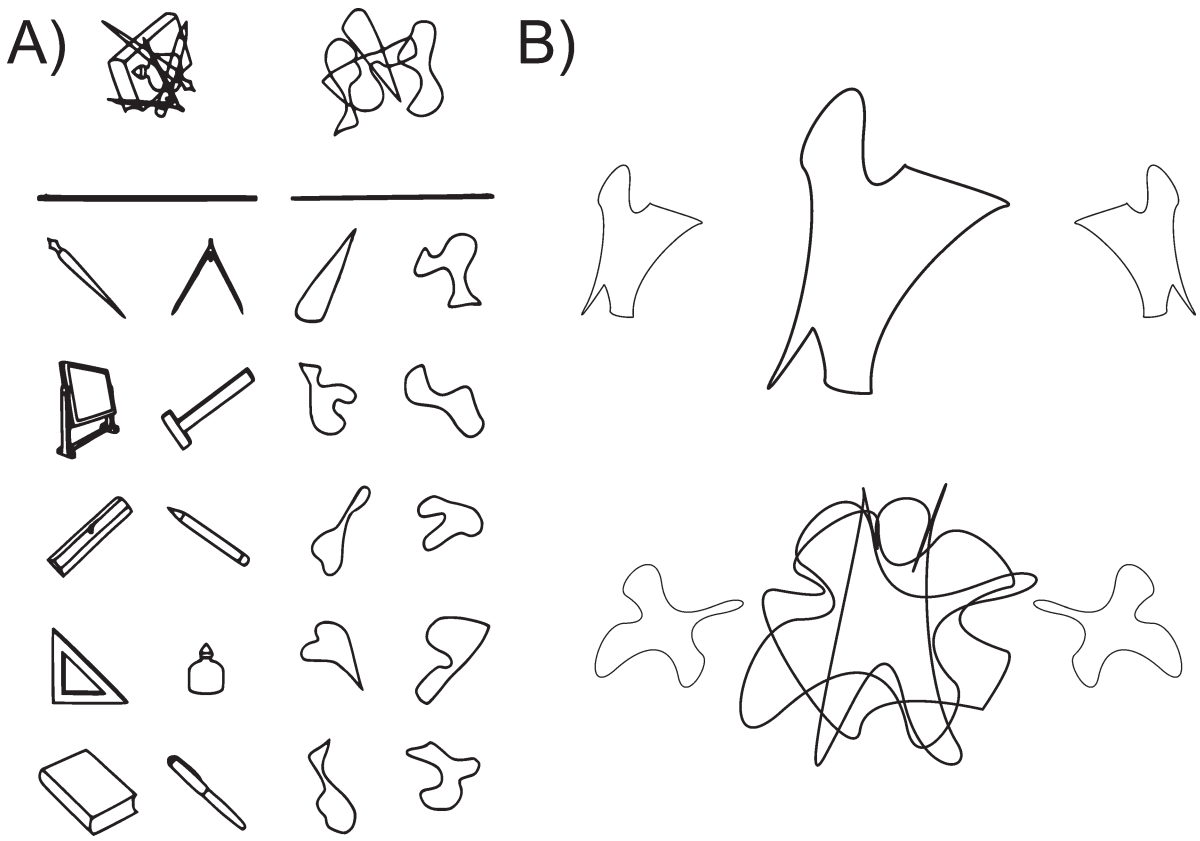

FIGURE 2. Sample stimuli from (A) the Overlapping Figures Test (Della Sala et al., 1995), and (B) our novel follow-up experiment (Experiments 2A and 2B). In the original task, participants identify all of the items occurring within the jumble of items at the top by pointing them out in the array at the bottom. In our task, participants decided whether the left or right item occurred in the central position, obscured (bottom) or not (top). Note that when the stimuli were presented to participants in our experiment the items were blue rather than black.

Participants were asked to point out the response alternatives that appeared in the overlapping set.

Results

Raw scores on the Overlapping Figures Test were compared to age- and education-based predictions from a normative model fit by the originating authors, and difference scores reflected the predicted and observed scores for all participants (see Fig. 3A). Group-level differences were evaluated using an ANOVA. Overall performance between groups was not reliably different by this test ($F(2, 12) = 1.513$, $P = 0.260$), and within overall performance, neither novel ($F(2,12) = 1.408$, $P = 0.282$) nor familiar ($F(2, 12) = 1.824$, $P > 0.203$) subsets were reliably different. Despite the lack of statistically reliable effects, inspection of individual scores revealed two qualitative patterns. First, both NCs and BDCs performed near ceiling, reflecting the limited sensitivity of the test: 4/5 NCs missed zero or one items; and 4/5 BDCs missed two or fewer items (see Table 3). Second, MTL patients showed a markedly different pattern, with 4/5 patients missing three or more items. Notably, these errors were numerically concentrated in the trials depicting novel items, with patients underperforming predictions by an average of 4.5 items for novel trials versus 1.7 items for familiar trials, although that difference was not reliable ($T(5.023) = 0.904$, $P = 0.407$).

Discussion

Although Experiment 2A did not yield reliable differences in group performance, most MTL patients did exhibit numerical decrements versus predicted performance, while most comparison participants did not. These numerical differences were most apparent in trials using novel shapes, and we decided to pursue a robust difference in performance using a task of our own design that borrowed important characteristics of the neuropsychological test. In Experiment 2B, we parametrically varied rotation and degree of overlap, employing many trials per condition in order to enhance the sensitivity of our test.

EXPERIMENT 2B

Participants

MTL and NC participants were as above, and 8 BDCs also completed the task (see Table 2).

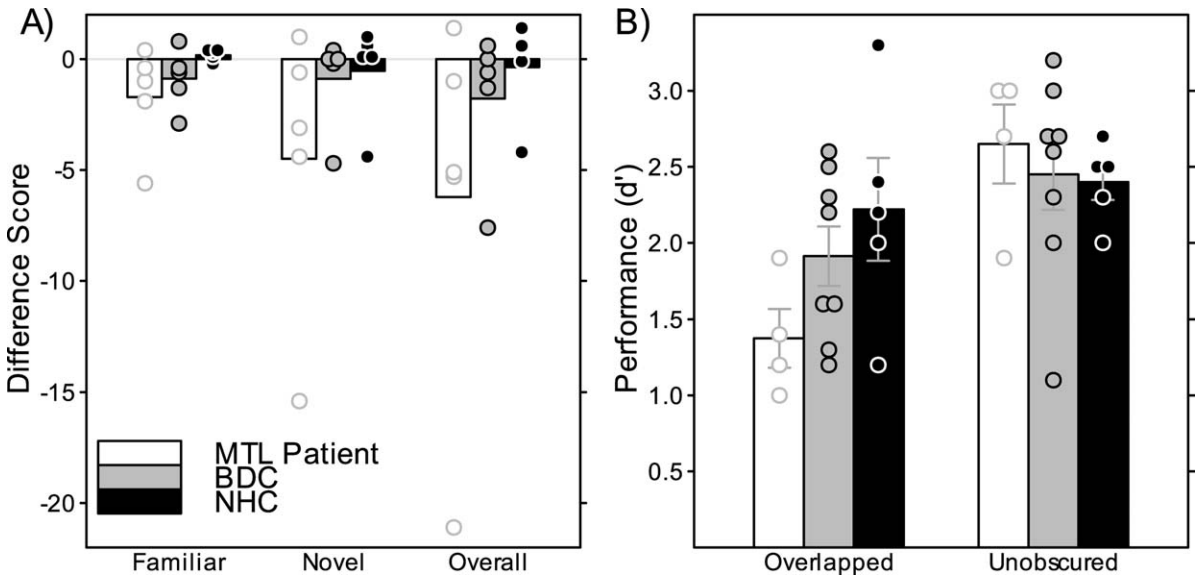

FIGURE 3. Plots of group mean (bars) and individual (points) performance on (A) the Overlapping Figures Test and (B) our novel follow-up experiment (Experiments 2A and 2B). Some MTL patients exhibited unusual impairments in the original OFT, especially with novel items. In our task, patients with hippocampal damage were impaired relative to comparisons when target items were obscured. Whiskers indicate ± 1 s.e.m.

Materials

Novel, randomly-generated outline figures were used as the stimuli in this experiment (see Fig. 2B). The area contained within each figure was roughly equated; no figure varied by more than 5% from the mean area.

Task

The participant's task was constant across the eight hybrid conditions in our 2 × 4 design (i.e., choose between two laterally presented response alternatives, one of which was present in some form at the center of the screen). We varied two conditions: the orientation of the correct response alternative either matched the center target item or differed by 90°; and the target item could appear in the center by itself or overlapped by one, two, or three obscuring items. Irrespective of orientation, the correct response alternative was 50% of the target's size but otherwise identical, while the lure response alternative was a mirror-reverse of the correct alternative. Participants completed one practice trial introducing each condition's format followed by 40 test trials per condition. No time limit was enforced on responses. When participants chose the incorrect response, the test display persisted until they made the correct response, but no other feedback was provided.

Results

Neither MTL patient 1846 nor BDC 3319 were able to comprehend the instructions for the rotated condition of the task, a deficit which was noted at the time of administration. The data of those two patients were therefore excluded from the analysis. We calculated a measure of discriminability (2AFC d′) based on raw performance (see Fig. 3B), using a standard correction for perfect performance [i.e., 1 – 1/(2 × no. trials)]. Data were analyzed by using a 2 × 4 repeated-measures ANOVA implemented as a linear mixed model. The presence of overlapping items was indicated by a binary predictor, and matching or mismatching rotation of the target and the correct response alternative was indicated by another binary predictor. Group membership was treated as a subject-level predictor with three levels: MTL; BDC; and NC. No reliable dif-

TABLE 3.

Overlapping Figures Task

		item type		
Patient ID	Group	Novel	Familiar	Overall
1846	MTL	−4.355	−0.961	−5.321
1951	MTL	−0.604	−0.415	−1.026
2308	MTL	−3.102	−1.943	−5.053
2363	MTL	−15.435	−5.609	−21.053
2563	MTL	1.019	0.35	1.363
1846c	NC	0.123	−0.208	−0.092
1951c	NC	0.096	0.393	0.481
2308c	NC	1.019	0.350	1.363
2363c	NC	0.553	0.060	0.606
2563c	NC	−4.434	0.275	−4.166
3319	BDC	−4.686	−2.915	−7.607
3137	BDC	0.396	−0.415	−0.026
0297	BDC	−0.199	0.836	0.63
3223	BDC	0.020	−1.272	−1.258
3093	BDC	0.019	−0.650	−0.637

Performance by all participants on the Overlapping Figures Task from Experiment 2A. Values indicate the difference between observed and model-predicted scores (i.e., negative numbers reflect impairment).

ferences were observed in overall group performance ($F(2,14) = 1.338$, $P = 0.294$), and all groups were affected by rotation ($F(1,98) = 388.879$, $P < 0.001$) and the number of overlapping items ($F(3,98) = 17.384$, $P < 0.001$). Crucially, while the consequences of rotation for performance were similar for all groups ($F(2,98) = 0.719$, $P = 0.490$), the number of overlapping items exerted a heterogeneous effect depending on group membership ($F(6,98) = 3.558$, $P < 0.005$). No other factors or interactions were reliable (each $P > 0.10$).

We followed up the ANOVA test with specific planned comparisons employing the same linear mixed model and corresponding linear contrasts. Comparing group-level performance across all conditions, MTL patients were reliably impaired relative to NCs ($Z = 3.324$, $P < 0.01$), but not BDCs ($Z = 2.139$, $P = 0.175$), while the two comparison groups did not differ ($Z = 0.167$, $P = 1.000$). Performance in conditions involving unobscured targets was marginally impaired when MTL patients were compared to NCs ($Z = 1.726$, $P = 0.084$) but not BDCs ($Z = 1.069$, $P = 0.285$), and the two comparison groups were indistinguishable ($Z = 0.048$, $P = 0.962$). However, across the conditions of interest wherein the target was overlapped by one or more distracters, MTL patients performed reliably less well than both NCs ($Z = 3.174$, $P < 0.005$) and BDCs ($Z = 2.095$, $P < 0.05$), while the two comparison groups did not differ ($Z = 0.209$, $P = 0.834$).

Discussion

The presence of overlapping distracter items selectively impeded MTL patients' performance in this task relative to both NCs and BDCs. The increased online representation demands of the overlapping conditions appear to require MTL structures for normal performance.

EXPERIMENT 3

Unlike the preceding experiments, our final task used a novel design requiring participants to identify fragmented outlines of common objects. Although this experiment superficially resembled a seminal study of non-declarative memory that also employed fragmented object outlines (Warrington and Weiskrantz, 1968), our task did not incrementally increase the proportion of the entire outline that was revealed across trials. Instead, participants were exposed to a sequence (Experiment 3A) or a set (Experiment 3B) of unique and complementary fragmented outlines from the same object (see Fig. 4), and asked to identify the item after each exposure based on all the information presented to that point.

EXPERIMENT 3A

Participants

MTL and NC participants were as above. One BDC participant discontinued participation after 11 trials owing to fatigue, and those data were not considered; 11 other BDCs completed the task (see Table 2).

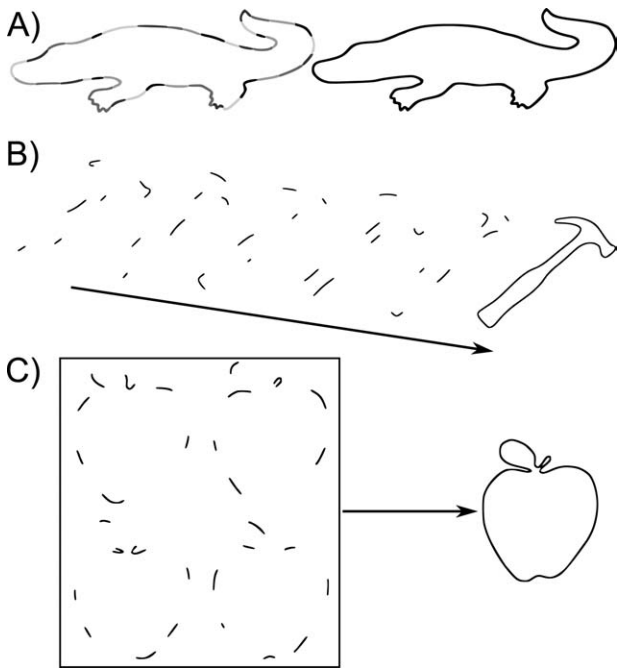

FIGURE 4. Sample stimuli from our novel experiment employing fragmented outlines (Experiments 3A and 3B). A: Illustrates the manner in which an outline was segmented into several non-overlapping fragmented outlines. B: Illustrates the sequential presentation of fragmentary outlines as in Experiment 3A. C: illustrates the simultaneous presentation used in Experiment 3B. Note that the items here have been modified slightly for illustration; in our experiments the outlines were one pixel wide, as in the originating work (De Winter and Wagemans, 2004, 2006, 2008).

Materials

The materials used in this experiment were derived from a thoroughly characterized set of object-outline stimuli (De Winter and Wagemans, 2004, 2006, 2008). We chose a subset of 64 highly recognizable outlines with high naming convergence according to normative data (De Winter and Wagemans, 2004). Every pixel of each outline had its curvature gauged by the originating authors, and those data were used to create the fragmented outlines used here. Following Biederman (1987), we recognized the importance of local maxima and minima of curvature to object perception. Therefore, each outline was divided into fragments extending from one local minimum to the next; each fragment contained a local maximum. Small, adjacent fragments were identified and combined using a clustering algorithm, and this process produced fragments of appropriate size. Fragmented outlines were created by choosing five unique, non-overlapping subsets of fragments from each object outline (see Fig. 4A). The order of fragmented outline presentation for each object was constant, but the order of object presentation varied between participants.

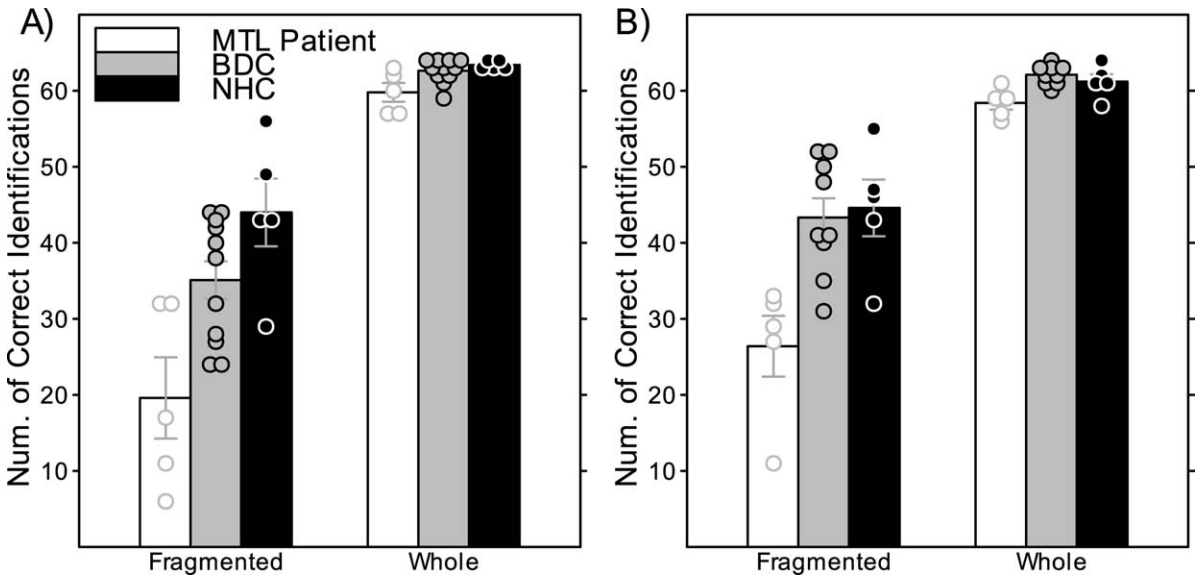

FIGURE 5. Plots of group mean (bars) and individual (points) performance in (A) Experiment 3A and (B) Experiment 3B. MTL patients performed reliably less well than comparisons when items were presented in fragmentary form. Whiskers indicate ±1 s.e.m.

Task

Participants were told that they would see part of the outline of an object and that they should identify the object as soon as possible. Every trial phase began with a 1-s fixation screen. Each fragmented outline was presented for 1 s followed by a grayscale noise mask for 500 ms, after which text instructions were superimposed on the noise mask; "Can you tell what the item is?" If the participant could not identify the object at this point, the trial was advanced to the next fragmented outline from the same object. Participants were encouraged to make as many responses per item as they cared to with no penalty, and responses were recorded in writing by the experimenter. Presentation of a given object's fragmented outlines proceeded until the correct response was made or the fifth fragmented outline had been presented. An explicit invitation to identify the object was extended after the presentation of the fifth fragmented outline if the participant did not volunteer a response. The final stage of every trial was the presentation of the object's complete outline; this allowed confirmation of a correct response or a final opportunity for identification. This whole-outline display was presented for 1 s (see Fig. 4B). Responses were scored correct if they appeared in normative naming data obtained from 45 college-age participants who viewed the entire object outline and reported the most common simple name for the object.

Results

Group-level differences in identification from sequentially presented fragmented outlines were evaluated in two conditions: based only on exposure to all five fragmented versions of an object's outline (fragmented); and after all fragmented outlines and the whole outline had been displayed (whole). In a first pass, raw correct identification scores from 64 items were used (see Fig. 5A). An ANOVA indicated that there were reliable differences between the groups, both the fragment ($F(2,18) = 8.469$, $P < 0.005$) and whole conditions ($F(2, 18) = 6.052$, $P < 0.01$). Planned comparisons between groups were conducted within each condition. Fragment-based identification by MTL patients was reliably impaired relative to NCs ($T(7.741) = 3.505$, $P < 0.01$) and to BDCs ($T(5.784) = 2.627$, $P < 0.05$); while NCs and BDCs did not differ ($T(6.601) = 1.750$, $P = 0.126$). Whole-item identification by MTL patients was likewise reliably impaired relative to healthy comparisons ($T(4.311) = 2.846$, $P < 0.05$); and marginally impaired relative to BDCs ($T(5.199) = 2.136$, $P = 0.084$); while NCs and BDCs did not differ ($T(13.636) = 1.435$, $P = 0.174$). The modest impairment in whole-item identification by MTL patients prompted us to conduct a follow-up analysis using proportional scores to correct fragment recognition for any impairment in whole-item recognition. Specifically, each participant's raw fragmented-outline identification score was divided by her/his whole-outline identification score to create a proportional score. An ANOVA of those proportional scores indicated group-level differences ($F(2,18) = 8.210$, $P < 0.005$), which were evaluated using planned comparisons between all groups. Once again, MTL patients were reliably impaired relative to NCs ($T(7.711) = 3.369$, $P < 0.05$) and to BDCs ($T(5.558) = 2.540$, $P < 0.05$); while NCs and BDCs did not differ ($T(6.327) = 1.715$, $P = 0.135$).

Discussion

Experiment 3A suggested that damage to the MTL may interfere with the ability to assemble sequentially presented information in a way that would aid identification. However, the task did require some brief maintenance of information within the sequence of fragmented outlines. We addressed this in

Experiment 3B, which presented four fragmented outlines simultaneously instead of five sequentially. Additionally, Experiment 3B allowed unlimited inspection time for whole outlines in order to avoid selectively disadvantaging participants who had not identified items based on fragmented outlines alone.

EXPERIMENT 3B

Participants

MTL and NC participants were as above, and 9 BDCs also completed the task (see Table 2).

Materials

The materials used in the simultaneous presentation experiment were similar to the materials employed in the sequential experiment, but we chose a new set of 64 items from the set provided by De Winter et al. that were not previously tested in Experiment 3A. This set was subjected to the same fragmenting procedure described previously except that four fragmented outline images were generated for each item instead of five.

Task

Participants were told that they would see four fragmented outline images simultaneously for 4 s and that all of the stimuli in a given display were derived from a single object's outline. Their task was to identify the single object during or after the presentation of the fragmented outlines. Participants were encouraged to give one or more responses, and to guess if they were uncertain. Responses were recorded, and then the whole object outline was presented for confirmation or correction (see Fig. 4C). Responses were scored correct if they appeared in normative naming data obtained from 45 college-age participants who viewed the entire object outline.

Results

Group-level differences in identification from simultaneously-presented fragmented outlines was evaluated in two conditions: based only on exposure to all fragmented versions of an object's outline (fragment); and after all fragmented outlines and the whole outline had been displayed (whole). In a first pass, raw correct identification scores from 64 items were used (see Fig. 5B). An ANOVA indicated that there were reliable differences between the groups, both the fragment ($F(2,16) = 8.472$, $P < 0.005$) and whole conditions ($F(2,16) = 7.661$, $P < 0.01$). Planned comparisons between groups were conducted within each condition. Fragment-based identification by MTL patients was reliably impaired relative to NCs ($T(7.961) = 3.333$, $P < 0.05$) and BDCs ($T(7.262) = 3.582$, $P < 0.01$); while NCs and BDCs did not differ ($T(7.718) = 0.282$, $P = 0.786$). Whole-item identification by MTL patients was only marginally impaired relative to NCs ($T(7.911) = 2.148$, $P = 0.064$); but reliably impaired relative to BDCs ($T(5.941) = 3.830$, $P < 0.01$); while NCs and BDCs did not differ ($T(5.568) = 0.861$, $P = 0.425$). As in Experiment 3A, the sometimes-reliable impairment in whole-item identification prompted us to conduct a control analysis using proportional scores to correct fragment identification for impairments in whole-item identification. An ANOVA of those proportional scores indicated group-level differences ($F(2,16) = 7.373$, $P < 0.01$), which were evaluated using planned comparisons between all groups. Once again, MTL patients were reliably impaired relative to NCs ($T(7.606) = 3.093$, $P < 0.05$) and to BDCs ($T(6.480) = 3.070$, $P < 0.05$); while NCs and BDCs did not differ ($T(7.849) = 0.462$, $P = 0.657$).

Discussion

Experiments 3A and 3B jointly show that damage to the MTL results in impairments in the ability to identify fragmented outlines of common objects, and a deficit in the ability to benefit from additional, complementary information (i.e., non-overlapping fragmented outlines). Impairment was observed irrespective of whether the complementary information was presented sequentially or simultaneously. Importantly, these effects of MTL damage appear to be dissociable from the generic effects of brain trauma. Patients with damage outside of the MTL did not differ reliably from NCs on any measure of fragmented outline identification, and showed better fragmented outline identification than MTL patients on all measures.

GENERAL DISCUSSION

We tested patients with MTL damage using a set of experiments that simultaneously presented all of the information necessary for accurate responses, and that may have benefited from relational representation. Despite putatively intact cognitive abilities, MTL patients were frequently impaired relative to healthy NCs. Furthermore, these deficits cannot be generally attributed to brain injury as MTL patients were also often impaired relative to BDCs. These results suggest that damage to the MTL impedes representation during intervals and with materials typically thought to be within the scope of working memory processes. Based on these findings, we submit that the hippocampus contributes similarly to cognition irrespective of the timescale, and that the structure's widely-acknowledged functions related to enduring memory are constantly influencing mental representations, including representations of novel materials.

Our MTL patient group included patients with focal hippocampal damage (1846, 2363, 2563) and patients with more extensive MTL damage (1951, 2308), and we did not observe any qualitative or reliable quantitative differences in the performance of focal hippocampal and MTL-extensive groups in any of our tasks. Further, we observed reliable impairments of our entire MTL patient group relative to both NCs and BDCs in four of five tasks, with qualitative evidence of some impairment in the fifth experiment. The inclusion of a BDC group is

crucial to any conclusion about the selective contributions of MTL structures to performance of our experimental tasks; otherwise, generic slowing of cognition owing to brain injury might confound our conclusions. We can therefore assert with some confidence that the impaired performance of patients confronted with the task of maintaining, comparing, discriminating, or apprehending complex stimuli may be attributable solely to hippocampal damage. This is not to imply that damage to other brain regions implicated in visuospatial processing would not also impact the performance of these tasks, but that hippocampal damage alone is sufficient to produce impairment.

We chose experimental tasks that had several common characteristics including the simultaneous or rapid sequential presentation of all necessary stimuli and the use of moderately complex novel or degraded familiar information. These shared features differentiate our tasks from those that MTL patients perform normally (e.g., digit-span tasks) that do not require a rich representation of the maintained material. While temporal order information must be preserved in digit-span tasks, the necessary rigidity of the stimulus representation means that a non-relational representation of the digits may support normal performance. A modified digit-span task requiring, for example, flexible access to specific digits, knowledge of the mode of presentation, or access to other contextual information, might well reveal differences between the representations maintained by healthy and MTL-lesion participants. Our tasks included two neuropsychological tests using materials that seemed likely to benefit from rich, relational representation, and several of the MTL patients were normatively impaired at these tasks in addition to any reported group-level differences in performance, despite generally intact intelligence as typically measured. This is particularly intriguing because dementia of the Alzheimer's type, a neurological disorder known to affect the hippocampus among other structures, has been shown to impair performance of both tasks (Della Sala et al., 1995; Jefferson et al., 2006). Our results suggest that hippocampal damage alone would account for some part of these task-specific deficits associated with Alzheimer's dementia.

Other authors have also reported impairment of MTL patient performance on tasks that do not involve delays. Lee et al., 2005a tested patients using a paradigm and stimuli borrowed from the animal-lesion literature (Buckley et al., 2001) which was an odd-man-out (OMO) task requiring participants to choose the unique item from an array containing multiple views of a lure item in addition to the singleton target. In the original work, macaques with perirhinal cortex lesions exhibited selective deficits in OMO problems involving complex but not simple materials (e.g., unimpaired at challenging color discrimination while impaired when discriminating two faces shown from different perspectives). Likewise, human patients with broad MTL lesions were selectively impaired when confronted with complex discrimination problems. Meanwhile, patients with focal hippocampal damage showed an even more selective pattern of sparing and impairment (i.e., these patients were impaired only when discriminating images of virtual scenes). Subsequent pairwise discrimination tasks (Lee et al., 2005b) and further OMO testing (Barense et al., 2007; Hartley et al., 2007) have generally supported these conclusions (but see Stark and Squire, 2000).

A critical difference between those reports and the current work is that none of our tasks involved the type of scene or scene-like stimuli common to those or other reports of impaired performance (Ryan and Cohen, 2004; Hannula et al. 2006; Olson et al., 2006; Cashdollar et al., 2009), but patients with isolated hippocampal damage still performed poorly. Another study using single items as memoranda (Nichols et al., 2006) reported that a mixed-etiology group of amnesic patients (including Korsakoff's, anoxia, and herpes simplex encephalitis) did not remember faces as well as healthy comparison participants at delays as of only 7 s, while ceiling effects prevented the rigorous evaluation of group-level differences at a 1 s delay. This outcome demonstrates the challenge of selecting tasks and materials that avoid perfect or chance performance in patient and comparison groups at extremely short delays.

Hippocampal involvement in online processing and representation aligns with other data and theoretical perspectives in the literature (cf., Jonides et al., 2008). In addition to studies of MTL-lesion patients, functional imaging has revealed hippocampal blood oxygen level dependent (BOLD) activation during active maintenance of information (Ranganath and D'Esposito, 2001; Stern et al., 2001; Olsen et al., 2009) over and above that due to encoding alone. Relational memory theory (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001) suggests that the hippocampus should enhance comparison and elaboration processes by forming relations among discrete elements being considered in turn. If this relational process would normally contribute to processing at the moment when information is being maintained and considered, then disruption of that relational process by hippocampal damage would make comparison and elaboration of maintained information more difficult. Borrowing from another theoretical perspective (Cowan, 2008), the hippocampus may facilitate the maintenance of information just outside the current contents of awareness and its relations with information in consciousness. Information in this state would be readily accessible and could potentially still influence ongoing processing without being the focus of attention. MTL damage would therefore be expected to impair the representation of relational information at any timescale.

The perceptual-mnemonic theory of MTL function (cf., Murray et al., 2007; Baxter, 2009; Graham et al., 2010) also predicts that MTL damage will lead to specific behavioral impairments at any timescale, although according to that theory the deficits are perceptual in nature rather than mnemonic. Many findings cited in support of the perceptual-mnemonic theory (e.g., Barense et al., 2005, 2007; Lee et al., 2005a,b) have frequently demonstrated deficits in visual discrimination tasks using complex, often spatial, stimuli, which would rely heavily on relational processing. Distinguishing the relational and perceptual-mnemonic perspectives will require experiments testing non-spatial online relational representation and patients with focal hippocampal lesions (e.g., Baddeley et al., 2010).

CONCLUSIONS

The hippocampus contributes to the online representation of complex, novel information, and even familiar information that has been rearranged or degraded to produce a novel presentation. This contribution relies on the well-characterized functions of the hippocampus that have generally been studied in the context of enduring memory. Relational memory theory may provide an explanation for the observed deficit as our findings indicate that flexible, hippocampal-dependent representations improve performance even over very brief intervals.

Acknowledgments

The authors thank Aashesh Verma and Jacob Gibbons.

REFERENCES

Allen JS, Tranel D, Bruss J, Damasio H. 2006. Correlations between regional brain volumes and memory performance in anoxia. J Clin Exp Neuropsychol 28:457–476.

Baddeley AD, Warrington EK. 1970. Amnesia and the distinction between long- and short-term memory. J Verb Learn Verb Behav 9:176–189.

Baddeley A, Allen R, Vargha-Khadem F. 2010. Is the hippocampus necessary for visual and verbal binding in working memory? Neuropsychologia 48:1089–1095.

Barense MD, Bussey TJ, Lee ACH, Rogers TT, Davies RR, Saksida LM, Murray EA, Graham KS. 2005. Functional specialization in the human medial temporal lobe. J Neurosci 25:10239–10246.

Barense MD, Gaffan D, Graham KS. 2007. The human medial temporal lobe processes online representations of complex objects. Neuropsychologia 45:2963–2974.

Baxter MG. 2009. Involvement of medial temporal lobe structures in memory and perception. Neuron 61:667–677.

Biederman I. 1987. Recognition-by-components: A theory of human image understanding. Psychol Rev 94:115–147.

Buckley MJ, Booth MCA, Rolls ET, Gaffan D. 2001. Selective perceptual impairments after perirhinal cortex ablation. J Neurosci 21:9824–9836.

Cashdollar N, Malecki U, Rugg-Gunn FJ, Duncan JS, Lavie N, Duzel E. 2009. Hippocampus-dependent and -independent theta-networks of active maintenance. Proc Natl Acad Sci USA 106:20493–20498.

Cave CB, Squire LR. 1992. Intact verbal and nonverbal short-term memory following damage to the human hippocampus. Hippocampus 2:151–163.

Cohen NJ, Squire LR. 1980. Preserved learning and retention of pattern-analyzing skill in amnesia—Dissociation of knowing how and knowing that. Science 210:207–210.

Cohen NJ, Eichenbaum H. 1993. Memory, Amnesia and the Hippocampal System. Cambridge, MA: MIT Press. 330 p.

Cowan N. 2008. What are the differences between long-term, short-term, and working memory? Prog Brain Res 169:323–338.

Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A. 2004. Neural systems behind word and concept retrieval. Cognition 92:179–229.

Davachi L, Dobbins IG. 2008. Declarative memory. Curr Dir Psychol Sci 17:112–118.

De Winter J, Wagemans J. 2004. Contour-based object identification and segmentation: Stimuli, norms and data, and software tools. Behav Res Methods Instrum Comput 36:604–624.

De Winter J, Wagemans J. 2006. Segmentation of object outlines into parts: A large-scale integrative study. Cognition 99:275–325.

De Winter J, Wagemans J. 2008. Perceptual saliency of points along the contour of everyday objects: A large-scale study. Percept Psychophys 70:50–64.

Della Sala S, Laiacona M, Spinnler H, Trivelli C. 1995. Poppelreuter-Ghent's Overlapping Figures Test: Its sensitivity to age, and its clinical use. Arch Clin Neuropsychol 10:511–534.

Drachman DA, Arbit J. 1966. Memory and the hippocampal complex. II. Is memory a multiple process? Arch Neurol 15:52–61.

Eichenbaum H, Cohen NJ. 2001. From Conditioning to Conscious Recollection: Memory Systems of the Brain. New York: Oxford University Press.

Eichenbaum H, Otto T, Cohen NJ. 1992. The hippocampus–What does it do. Behav Neural Biol 57:2–36.

Feinstein JS, Rudrauf D, Khalsa SS, Cassell MD, Bruss J, Grabowski TJ, Tranel D. 2010. Bilateral limbic system destruction in man. J Clin Exp Neuropsychol 32:88–106.

Graham KS, Barense MD, Lee AC. 2010. Going beyond LTM in the MTL: A synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. Neuropsychologia 48:831–853.

Hannula DE, Tranel D, Cohen NJ. 2006. The long and the short of it: Relational memory impairments in amnesia, even at short lags. J Neurosci 26:8352–8359.

Hartley T, Bird CM, Chan D, Cipolotti L, Husain M, Vargha-Khadem F, Burgess N. 2007. The hippocampus is required for short-term topographical memory in humans. Hippocampus 17:34–48.

Hooper HE. 1958. The Hooper Visual Organization Test: Manual. Los Angeles: Western Psychological Service.

Jefferson AL, Wong S, Bolen E, Ozonoff A, Green RC, Stern RA. 2006. Cognitive correlates of HVOT performance differ between individuals with mild cognitive impairment and normal controls. Arch Clin Neuropsychol 21:405–412.

Jonides J, Lewis RL, Nee DE, Lustig CA, Berman MG, Moore KS. 2008. The mind and brain of short-term memory. Annu Rev Psychol 59:193–224.

Lee ACH, Buckley MJ, Pegman SJ, Spiers H, Scahill VL, Gaffan D, Bussey TJ, Davies RR, Kapur N, Hodges JR, Graham KS. 2005a. Specialization in the medial temporal lobe for processing of objects and scenes. Hippocampus 15:782–797.

Lee ACH, Bussey TJ, Murray EA, Saksida LM, Epstein RA, Kapur N, Hodges JR, Graham KS. 2005b. Perceptual deficits in amnesia: Challenging the medial temporal lobe 'mnemonic' view. Neuropsychologia 43:1–11.

Murray EA, Bussey TJ, Saksida LM. 2007. Visual perception and memory: A new view of medical temporal lobe function in primates and rodents. Annu Rev Neurosci 30:99–122.

Nichols EA, Kao YC, Verfaellie M, Gabrieli JDE. 2006. Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. Hippocampus 16:604–616.

Olsen RK, Nichols EA, Chen J, Hunt JF, Glover GH, Gabrieli JD, Wagner AD. 2009. Performance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample. J Neurosci 29:11880–11890.

Olson IR, Page K, Moore KS, Chatterjee A, Verfaellie M. 2006. Working memory for conjunctions relies on the medial temporal lobe. J Neurosci 26:4596–4601.

Ranganath C. 2010. A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. Hippocampus 20:1263–1290.

Ranganath C, D'Esposito M. 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31:865–873.

Ryan JD, Cohen NJ. 2004. The nature of change detection and online representations of scenes. J Exp Psychol Hum Percept Perform 30:988–1015.

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11–21.

Sidman M, Stoddard LT, Mohr JP. 1968. Some additional quantitative observations of immediate memory in a patient with bilateral hippocampal lesions. Neuropsychologia 6:245–254.

Stark CEL, Squire LR. 2000. Intact visual perceptual discrimination in humans in the absence of perirhinal cortex. Learn Mem 7:273–278.

Stern CE, Sherman SJ, Kirchhoff BA, Hasselmo ME. 2001. Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. Hippocampus 11:337–346.

Warrington EK, Weiskrantz L. 1968. New method of testing long-term retention with special reference to amnesic patients. Nature 217:972–974.

Wechsler D. 1997a. Wechsler Adult Intelligence Scale–Third Edition. New York, New York: The Psychological Corporation.

Wechsler D. 1997b. Wechsler Memory Scale–Third Edition. New York, New York: The Psychological Corporation.

Wechsler D. 2008. Wechsler Adult Intelligence Scale-Fourth Edition. San Antonio, TX: Pearson.

Warrington EK, Baddeley AD. 1974. Amnesia and memory for visual location. Neuropsychologia 12:257–263.

Wickelgren WA. 1968. Sparing of short-term memory in an amnesic patient: Implications for strength theory of memory. Neuropsychologia 6:235–244.