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Lesions Affecting the Right Hippocampal Formation Differentially Impair Short-Term Memory of Spatial and Nonspatial Associations

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ABSTRACT: Converging evidence from behavioral and imaging studies suggests that within the human medial temporal lobe (MTL) the hippocampal formation may be particularly involved in recognition memory of associative information. However, it is unclear whether the hippocampal formation processes all types of associations or whether there is a specialization for processing of associations involving spatial information. Here, we investigated this issue in six patients with postsurgical lesions of the right MTL affecting the hippocampal formation and in ten healthy controls. Subjects performed a battery of delayed match-to-sample tasks with two delays (900/5,000 ms) and three set sizes. Subjects were requested to remember either single features (colors, locations, shapes, letters) or feature associations (color-location, color-shape, color-letter). In the single-feature conditions, performance of patients did not differ from controls. In the association conditions, a significant delay-dependent deficit in memory of color-location associations was found. This deficit was largely independent of set size. By contrast, performance in the color-shape and color-letter conditions was normal. These findings support the hypothesis that a region within the right MTL, presumably the hippocampal formation, does not equally support all kinds of visual memory but rather has a bias for processing of associations involving spatial information. Recruitment of this region during memory tasks appears to depend both on processing type (associative/nonassociative) and to-be-remembered material (spatial/nonspatial). © 2010 Wiley-Liss, Inc.

KEY WORDS: associative memory; relational memory; short-term memory; medial temporal lobe; hippocampus

INTRODUCTION

It is well-established in neuroscience that the Medial Temporal Lobe (MTL) is an essential structure for conscious memory of facts and events. It consists of the hippocampal formation (i.e., hippocampus, dentate gyrus, subiculum, presubiculum, parasubiculum and the entorhinal cortex) and the perihinal and parahippocampal cortices (Insausti and Amaral, 2004; Amaral and Lavenex, 2007). Behavioral research in humans and animals has pointed to a division of labor between MTL subregions (Squire et al., 2004; Davachi, 2006; Eichenbaum et al., 2007; Morris, 2007; Murray et al., 2007). Although their respective contributions to perception and memory are still under debate, several theories of MTL function converge on the idea that the hippocampal formation is particularly involved in processing of associations between stimuli or stimulus features (Squire et al., 2004; Davachi, 2006; Eichenbaum et al., 2007; Mayes et al., 2007; Morris, 2007).

For example, being one of the first accounts of hippocampal function, the cognitive map theory suggests that the hippocampus is particularly implicated in processing information on places and paths, i.e., spatial associative information (O'Keefe and Nadel, 1978; Burgess et al., 2002). While the observation of visuospatial associative memory deficits in humans with MTL damage is consistent with this theory (e.g., Smith and Milner, 1981, 1989; Owen et al., 1995, 1996; Crane and Milner, 2005; Olson et al., 2006; Hartley et al., 2007; Varga-Khadem et al., 2007; Braun et al., 2008; Finke et al., 2008), several studies on humans with MTL lesions involving the hippocampal formation have revealed associative memory deficits which are clearly nonspatial, such as memory for word pairs, face pairs, face-word pairs, or pairs of visual objects (e.g., Kroll et al., 1996; Giovanello et al., 2003; Turriziani et al., 2004; Varga-Khadem et al., 2007). These results therefore support a broader role of the hippocampal formation in mediating all manner of associations, regardless of the stimulus material, as suggested by the relational theory (Cohen and Eichenbaum, 1993; Eichenbaum, 2004). This account of hippocampal function is further corroborated by hippocampal activation during memory of nonspatial associations in several functional imaging studies (e.g., Henke et al., 1997, 1999a; Miller et al., 2008; Staresina and Davachi, 2008; Troyer et al., 2008).

Few imaging and patient studies, however, have directly compared contributions of the human hippocampal formation to processing of spatial and nonspatial associative information. While some results from such studies are compatible with a relative specialization of the hippocampal formation for perception and memory of spatial relations (Kumaran and Maguire,

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TABLE 1.

Patient Data and Individual Lesion Extents

	Age (yrs)	Pre-OP epilepsy (months)	Post-OP time (months)	Lesion extent				
				HIP	ERC	PRC	PHC	ITC
AM	33	37	60	+	+	++	0	0
DB	23	27	4	++	++	+	+	0
FP	25	13	15	+	++	++	0	0
HN	43	3	39	+	+	+	0	0
SD	25	39	60	++	++	++	+	++
SW	21	26	65	++	++	++	0	0

HIP, hippocampus; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex; ITC, infero-temporal cortex; "0" indicates an unaffected subregion, "+" a rostro-caudal lesion extent up to 20 mm, and "++" up to 40 mm.

2005; Lee et al., 2005; Graham et al., 2006; Piekema et al., 2006), studies in amnesic patients have repeatedly demonstrated almost equal impairments across spatial and nonspatial associative tasks (Hannula et al., 2006; Konkel et al., 2008).

Here, we have studied associative memory in a group of six patients with postsurgical lesions of the right MTL affecting the hippocampal formation. In our previous investigations in five of these patients (Braun et al., 2008; Finke et al., 2008), it was not clear whether the observed deficit in short-term memory for color-location associations reflected a general impairment in associative memory, or whether it depended on the cross-modality of the to-be remembered associations, or whether it depended on the spatial component of the associative stimulus material. A set of seven delayed match-to-sample tasks was used, in which subjects were requested to remember nonassociative stimuli as well as spatial and nonspatial associations. We aimed to investigate whether associative short-term memory functions of the right hippocampal formation are dependent on the stimulus material.

MATERIALS AND METHODS

Participants

Six patients (age 28.3 ± 3.4 yrs) were recruited from the Department of Neurosurgery at the Charité-Universitätsmedizin Berlin, Germany (Table 1). All had undergone resection of right MTL structures for the treatment of benign brain tumors causing epilepsy (Fig. 1). Five patients had already participated in previous experiments of our lab (patients A.M., F.P., H.N., S.D. and S.W., see Braun et al., 2008; Finke et al., 2008 for MRIs and individual patient characteristics). Patient D.B., a 23-yr-old female with a resected ganglioglioma was added to this group. Mean duration of preoperative epilepsy was 24.2 ± 5.7 months, mean delay between operation and testing 40.5 ± 10.6 months. Seizures had ceased postoperatively in all patients and they were back in their professional and social lives. Patients were free of additional neurological or psychiatric disorders and had normal or corrected-to-normal vision. All patients received anticonvulsant medication in regular dosages. Four days of testing were required in each participant for completion of the experiments. As it was difficult to recruit a sufficient number of control subjects who could spare this much time for testing, we used two control groups of 10 healthy subjects each (control Group A: age 34.5 ± 4.8 yrs; control Group B: age 28.6 ± 3.2 yrs). There were no significant differences between patient and control groups in terms of age (Kruskal-Wallis-test, $df = 2$, $\chi^2 = 0.7$, $P = 0.70$) and years of education (patients: 13.3 ± 0.8 yrs; control Group A: 14.1 ± 0.5 yrs; control Group B: 14.4 ± 0.6 yrs; $df = 2$, $\chi^2 = 2.6$, $P = 0.27$). Groups were furthermore matched on the basis of verbal intelligence as assessed by MWT-B, a German equivalent to the National Adult Reading Test (Lehrl, 2005). There was no significant difference of verbal IQ between groups (patients: 107.2 ± 4.5; control Group A: 109.0 ± 3.4; control Group B: 108.7 ± 4.8; $df = 2$, $\chi^2 = 0.3$, $P = 0.88$). Nonverbal intelligence was evaluated by subtest No. 3 of LPS, a German equivalent to Raven's Progressive matrices (Horn, 1983). Again, there were no significant differences in LPS-scores (t-values) between groups (patients: 57.5 ± 3.5; control Group A: 58.2 ± 2.2; control Group B: 61.0 ± 1.9; $df = 2$, $\chi^2 = 1.7$, $P = 0.43$). Informed consent was obtained from each subject before participation in the study that was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

Lesion Evaluation

In patients, structural magnetic resonance imaging was performed with a three-dimensional gradient echo sequence to obtain isotropic volume elements of 1 mm^3. Covering the temporal lobes, 80–100 coronal sections of 1 mm thickness each were reconstructed in perpendicular orientation to the line connecting anterior and posterior commissures. Individual extent of damage to different subregions of the MTL (amygdala, hippocampus, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and infero-temporal cortex) was then determined by identifying

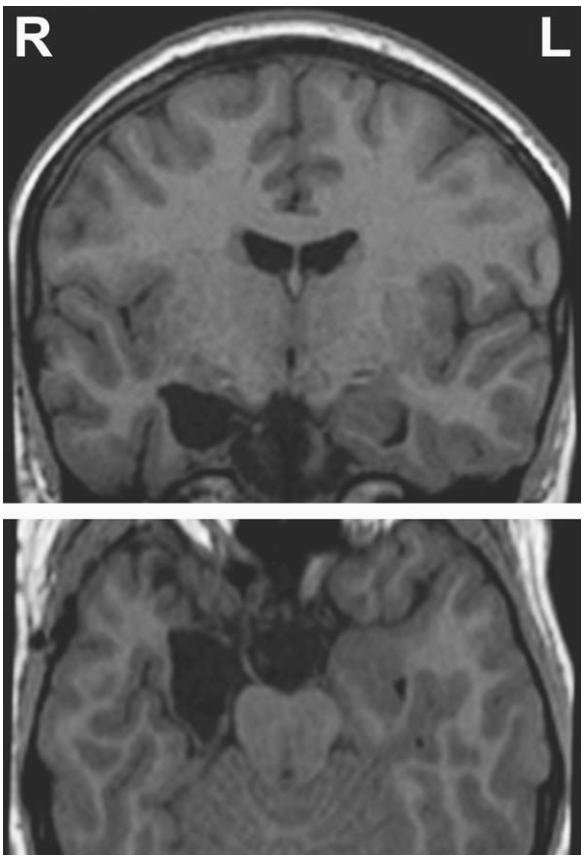

FIGURE 1. Example lesion, patient D.B. Top: coronal MRI section perpendicular to the line connecting the anterior and posterior commissures (AC-PC line), at the level of amygdala, hippocampal head, rostral entorhinal cortex, rostral perirhinal cortex and infero-temporal cortex. Bottom: Axial MRI section parallel below the AC-PC line, at the level of amygdala, rostral hippocampus, entorhinal cortex, perirhinal cortex and infero-temporal cortex. Note damage to rostral hippocampus and adjacent MTL structures on the right.

anatomical landmarks according to Braun et al. (2008). All patients had damage to the right amygdala, anterior hippocampus, anterior entorhinal cortex, and portions of perirhinal cortex (Table 1). One patient had slight additional damage to the anterior parahippocampal cortex and in another patient, parahippocampal and inferotemporal cortices were affected by the neurosurgical operation. In the four remaining patients, parahippocampal and inferotemporal cortices were intact.

Paradigms and Procedure

Subjects sat in a darkened room in front of a 22-in. computer monitor while their head was positioned on a chinrest to ensure a constant viewing distance of 50 cm to the screen. Seven delayed-match-to-sample tasks with memory delays of 900 and 5,000 ms were used to test nonassociative and spatial and nonspatial associative memory (Figs. 2A–F). While subjects fixated on a small central dot, a sample array of two to six simultaneously appearing stimuli was presented for 200 ms. After an unfilled memory delay of unpredictable length (900 or 5,000 ms), a single probe stimulus was presented for up to 2,000 ms. Subjects indicated by an unspeeded manual key press whether this probe matched one of the sample stimuli in color, location, shape, or letter identity (nonassociative tasks; Figs. 2A–D), or in conjunction of color and location, color and shape or color and letter (associative tasks; Figs. 2E–G). Visual stimuli were programmed with ERTS software (BeriSoft, Germany) and were presented on a light gray background (luminance: 21 cd m^{-2}) within a central region of the screen ($9.8^\circ \times 7.3^\circ$ of visual angle). Maximal stimulus size was $1^\circ \times 1^\circ$ with a minimal distance of 2° between stimuli. Except for the location and color-location tasks (Figs. 2B,E), sample stimuli were presented at locations equally spaced around the central dot. Nine easily discriminable colors (red, orange, yellow, green, cyan, blue, violet, white, and black) were used for the color task and the association tasks (Figs. 2A,E–G). Each color appeared only once in a given stimulus array. The color task (Fig. 2A) featured simple colored dots. Stimuli in the location (Fig. 2B) task were plain dark gray squares that could randomly appear at 48 possible locations on the screen. For the shape task (Fig. 2C), nine different stimuli were designed to be easy to discriminate yet difficult to verbalize when appearing in combination as a sample. Stimuli included a cross, an unfilled square, a triangle, a circle, a rotated "T" and two rotated "L" shapes as well as two open ('three-sided') squares. In the letter task (Fig. 2D), we used all letters of the Latin alphabet excluding vowels and German umlauts (to avoid the accidental formation of words) as well as the letter "Y" (since its German name "yp·si·lon" is the only one to have more than one syllable).

With the exception of the location and color-location tasks, all tasks were modifications of the tasks used in Finke et al. (2008) and Braun et al. (2008). However, in pilot experiments on normal subjects with the variants described here, the overall difficulty proved to be very different between tasks when the original parameters (sample presentation time, delay lengths, set sizes) were used. Ceiling effects occurred in some conditions while performance was at chance level in others. Hence, difficulty needed to be adjusted in each task so that ceiling effects were avoided and control subjects could perform well above chance level at the largest set size in every task. In a previous study with the original tasks (Finke et al., 2008), the effect of set size on memory performance was shown to be independent of task and delay length. Therefore, we decided to adjust task difficulty primarily by varying set size (color, shape, and letter tasks: 3, 4, 5 stimuli; color-shape and color-letter tasks: 2, 3, 4 stimuli; location and color-location tasks: 2, 4, 6 stimuli). To retain comparability of tasks, we did not vary other parameters such as the duration of stimulus presentation or delay length. For each task, the three set sizes were administered in separate blocks of 24 trials in pseudorandom order with an equal number of short/long delays and match/nonmatch trials. Tasks were run in counterbalanced order on 2 of 4 days of testing with short training blocks prior to recording. In total, subjects performed 288 trials per task. Fixation was monitored by video-oculography (iView Hi-Speed, SMI, Germany) in all but one patient and in 15 out of 20 controls.

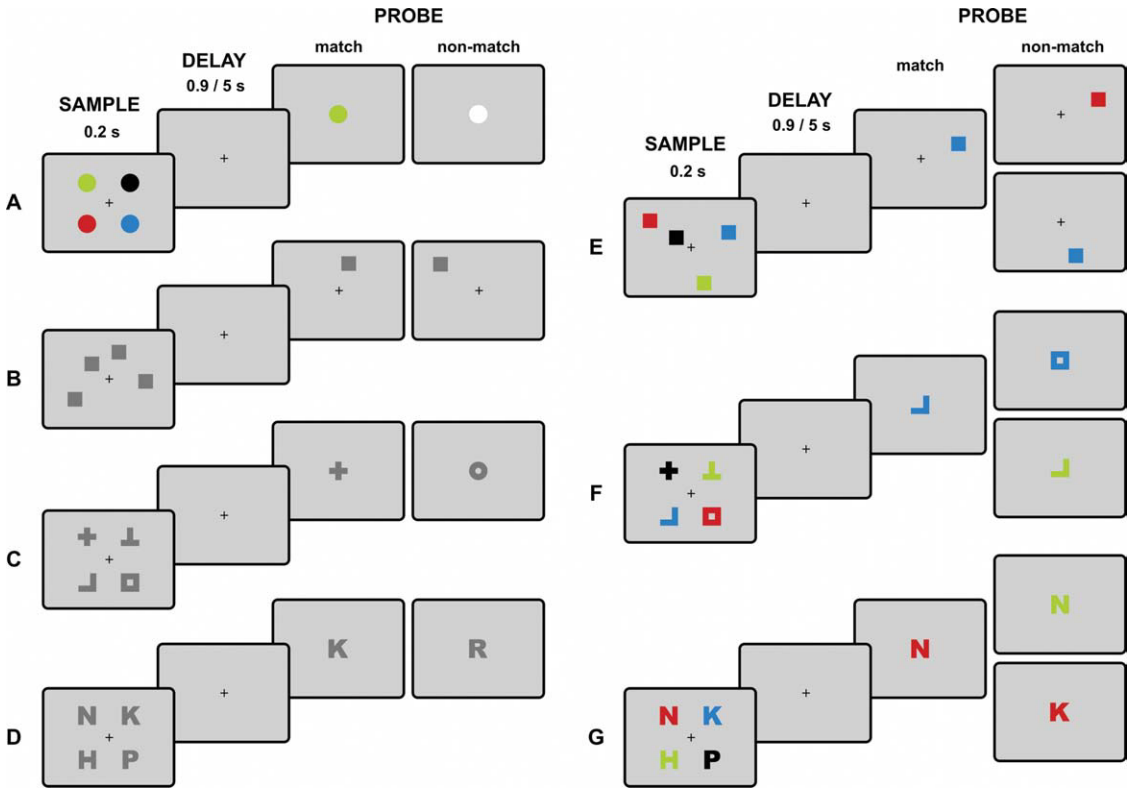

FIGURE 2. Schematic of the seven DMS tasks. (A–D) nonassociative tasks: (A) color task; (B) location task; (C) shape task; (D) letter task; (E–G) associative tasks: (E) color-location task; (F) color-shape task; (G) color-letter task. While fixating on a central fixation cross, subjects were presented an array of visual stimuli. After a memory delay of unpredictable length (900 or 5,000 ms), a single probe stimulus appeared and subjects indicated by a key press whether or not the probe matched one of the sample stimuli in color (A), location (B), shape (C), letter identity (D), color and location (E), color and shape (F), color and letter identity (G). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Data Analysis

Patients and controls kept fixating on the center of the screen in the majority of trials. Eye positions outside a radius of 1° of visual angle around the central fixation dot did occur but the difference between patients and controls was not significant (patients: 2% of all trials, controls: 9% of all trials; $P > 0.05$). Trials with interrupted fixation were not repeated. For each task, delay and set size, performance was expressed both in percent correct and d' scores (Macmillan and Creelman, 2005). Since results were not different when using either measure of performance for statistical analysis, percent correct scores are reported. As the number of subjects permitted no meaningful conclusions on the normality of the data distribution, nonparametric statistical tests were applied throughout (Altman, 1991).

RESULTS

Nonassociative Tasks

Group results are shown in Figure 3. Performance was clearly above chance level in each task and each group. However, inspection of Figure 3 also reveals performance differences between tasks. In controls, significant differences between tasks were found (collapsed over delays and set sizes; Friedman-analysis of variance (ANOVA), $df = 3$, $\chi^2 = 18.16$, $P < 0.001$). Performance in the letter task was significantly above performance in the color, location, and shape tasks (collapsed over delays and set sizes; Wilcoxon-test, $P \leq 0.04$ for all comparisons), and performance in the shape task was inferior to performance in the in the color, location, and letter tasks (collapsed over delays and set sizes; Wilcoxon-test, $P \leq 0.02$ for all comparisons). Performance between the color and location tasks did not differ (collapsed over delays and set sizes; Wilcoxon-test, $P = 0.41$). While these analyses indicate some differences in adjustment of task difficulty between conditions, performance between groups did not differ significantly. In the color task, no significant effect of the factor group was found in overall performance (collapsed over delays and set sizes; Mann-Whitney-test, $P = 0.09$). However, the effect of delay was significant (performance collapsed over groups and set sizes; Wilcoxon-test, $P = 0.003$), indicating that performance changed as the delay length increased. Similar results were obtained in the location task and the shape task. Again, there was no significant effect of the factor group (location: $P = 0.37$; shape: $P = 0.56$) whereas the effect of delay was

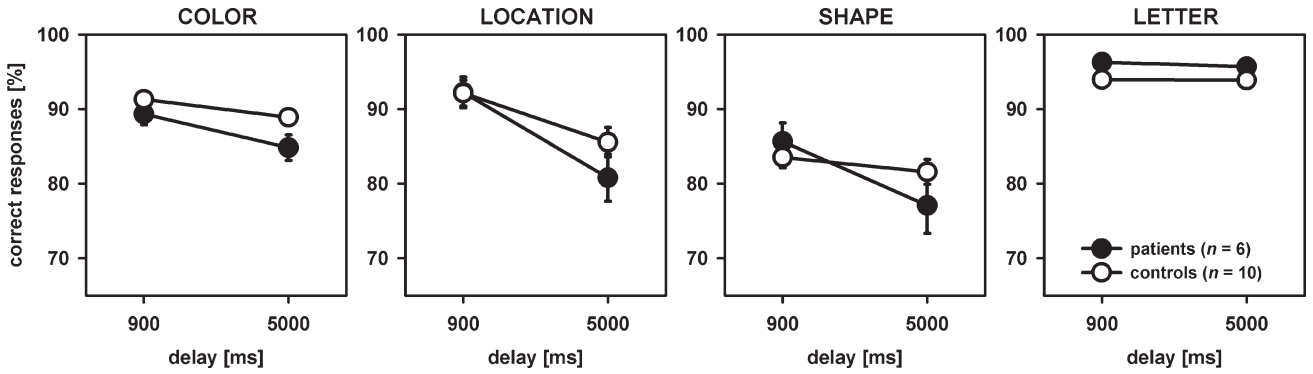

FIGURE 3. Nonassociative tasks, group results. Average performance of controls (unfilled circles) and patients (filled circles). Mean correct responses in percent ± s.e.m, shown as a function of delay.

significant both in the location task ($P = 0.001$) and the shape task ($P = 0.001$). In the letter task, performance was slightly different. Here, neither the factor group nor the factor delay was significant ($P = 0.12$ and 0.59, respectively), suggesting that all subjects could easily retain letter stimuli for a delay of up to 5,000 ms.

Associative Tasks

Group results are shown in Figure 4. Performance was clearly above chance level in each task and each group. Inspection of Figure 4 also reveals that performance of controls was similar across tasks ($df = 2$, $\chi^2 = 3.8$, $P = 0.15$), indicating comparable adjustment of task difficulty between conditions. However, unlike in the nonassociative tasks, clear differences between groups were observed. In the color-location task, a significant effect of the factor group on overall performance was found ($P = 0.003$). Whereas controls showed no significant effect of delay ($P = 0.59$), patients' performance deteriorated from 900 to 5,000-ms delay ($P = 0.03$). Comparing the performance of patients and controls, we found no significant difference between both groups at 900-ms delay (performance collapsed over set sizes; patients: 83.6%, controls: 88.3%, Mann-Whitney-test, $P = 0.07$) but a significant difference at 5,000-ms delay (patients: 74.3%, controls: 87.3%, $P = 0.001$). These analyses indicate that patients performed worse compared to controls as the length of the memory delay increased from 900 to 5,000 ms. A significant influence of set size on task performance was present both in the control group (collapsed over delays; Friedman-ANOVA, $df = 2$, $\chi^2 = 20.0$, $P < 0.001$) and in the patient group at both delays (900 ms: $df = 2$, $\chi^2 = 12.0$, $P = 0.002$; 5,000 ms: $df = 2$, $\chi^2 = 10.2$, $P = 0.006$). Further post hoc testing revealed that performance at 5,000-ms delay was significantly different between patients and controls at all three set sizes (two stimuli: patients 89.9%, controls 98.1%, Mann-Whitney-test, $P = 0.02$; 4 stimuli: patients 69.4%, controls 86.5%, $P = 0.007$; six stimuli: patients 63.5%, controls 77.3%, $P = 0.001$). This highlights that the patients' memory deficit appeared irrespective of the number of to-be-remembered stimuli. In addition, in the color-location task, performance of controls was on a similar level as in the related nonassociative tasks, i.e., the color and location tasks (performance collapsed over array sizes; 900 ms: Kruskal-Wallis-test, $df = 2$, $\chi^2 = 4.1$, $P = 0.13$; 5,000 ms: $df = 2$,

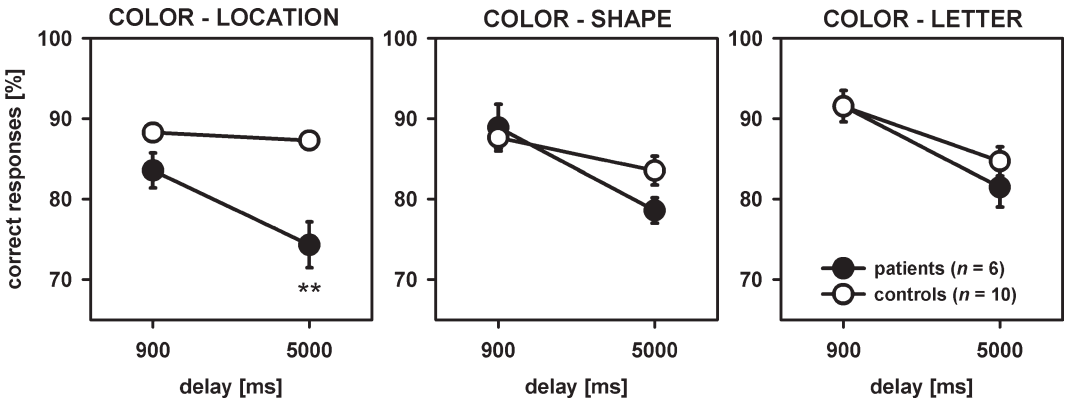

FIGURE 4. Associative tasks, group results. Average performance of controls (unfilled circles) and patients (filled circles). Mean correct responses in percent ± s.e.m, shown as a function of delay. $^{**}P = 0.001$ difference between groups.

$\chi^2 = 2.5$, $P = 0.28$). This fact argues against the speculation that the selectivity of our patients' memory deficit might be caused by a greater difficulty of the color-location task.

The two nonspatial association tasks, i.e., the color-shape task and the color-letter task, yielded results that were distinct from the color-location task. Similar to the nonassociative single-feature tasks mentioned above, we observed no significant effect of the factor group (color-shape: $P = 0.37$, color-letter: $P = 0.71$) whereas the influence of delay was significant in both tasks (color-shape: $P = 0.008$; color-letter: $P = 0.001$). In addition, performance between these two nonspatial association tasks did not differ significantly (performance collapsed over groups and set sizes; 900 ms: Mann-Whitney-test, $P = 0.06$; 5,000 ms: $P = 0.42$). Confirming our previous assumption, increasing array sizes did invariably cause a statistically significant drop in group average performance in all seven tasks, irrespective of delay (Friedman-ANOVAs, all P-values <0.006).

DISCUSSION

The present study investigated the role of the right MTL for human associative memory in patients with postsurgical lesions affecting the right hippocampal formation. The experimental design of our investigation complemented previous lesion studies by the choice of a patient model with well-defined anatomical lesion borders, a systematic comparison of multiple nonassociative and associative memory tasks involving spatial and nonspatial stimulus material, an experimental design that minimized differences in perceptual and mnemonic demands across tasks, and control of eye movement-based rehearsal strategies. Extending earlier observations (e.g., Hannula et al., 2006; Olson et al., 2006; Braun et al., 2008; Finke et al., 2008), our patients showed no deficits in nonassociative short-term memory tasks, thus supporting the hypothesis that memory representations that depend on the integrity of the hippocampal formation are mainly associative (Davachi, 2006; Eichenbaum et al., 2007; Mayes et al., 2007; Morris, 2007). However, our results further suggest that the right hippocampal formation does not equally support all types of visual associative memory. Although it seems premature to infer from a limited battery of delayed match-to-sample tasks on the entirety of possible short-term memoranda supported by the affected MTL subregions of our patients, our findings are best explained by a bias of the right hippocampal formation for memory of associations involving spatial information.

Brain–Behavior Relationships With Postsurgical Lesions to the MTL

Damage to the right MTL in our patients was circumscribed, but not confined to the hippocampus and entorhinal cortex. Small portions of perirhinal cortex were involved in all cases. It is therefore not possible to unequivocally relate our patients' deficits to a distinct subregion within this common lesion zone. However, the extrinsic connectivity of the hippocampal formation and of the perirhinal cortex differ considerably in primates, with only the former receiving direct inputs from brain regions involved in spatial cognition (Goldman-Rakic, Selemon and Schwartz, 1984; Cavada and Goldman-Rakic, 1989; Suzuki and Amaral, 1990, 1994a,b). In addition, several functional imaging studies that investigated MTL activation during visuo-spatial associative memory tasks found predominant activation of the hippocampal formation as compared to perirhinal cortex (e.g., Duzel et al., 2003; Piekema et al., 2006; Rauchs et al., 2008; Ryan et al., 2009). The hypothesis appears therefore justified that—within the affected right-sided MTL subregions of our patients—lesion to the hippocampal formation is mainly responsible for the observed behavioral deficit.

A major difference between our approach and several preceding human and animal lesion studies is the fact that left MTL structures were unaffected in our patients. The material-specificity of the observed deficits may thus at least partly result from hemispheric asymmetries for processing of visuo-spatial associations. Several studies in patients with unilateral postsurgical lesions of the MTL have reported visuo-spatial memory deficits with right-sided lesions, but no or only minor deficits with left-sided lesions (Smith and Milner, 1981, 1989; Feigenbaum et al., 1996; Abrahams et al., 1997; Bohbot et al., 1998; Spiers et al., 2001; Stepankova et al., 2004; Crane and Milner, 2005). Others found almost equal impairments in tasks requiring visuo-spatial memory with right- and left-sided lesions (Owen et al., 1995, 1996; Astur et al., 2002; Kessels et al., 2004; Glikmann-Johnston et al., 2008). Most patients in these studies were operated for medically intractable epilepsy associated to hippocampal sclerosis. Facing the likelihood of brain reorganization with this disorder (Hermann et al., 1992; Seidenberg et al., 1998; Martin et al., 2002; Braun et al., 2008) and the developmental abnormalities that may cooccur with the syndrome of temporal lobe epilepsy with hippocampal sclerosis (Duzel et al., 2006), a direct comparison to our patients may be confounded by adaptive processes within and across hemispheres that may be less relevant in MTL disorders acquired after infancy (Elger et al., 2004). In addition, differences in collateral damage to cortices outside the MTL may significantly modify patterns of cognitive impairment with unilateral MTL removals (Helmstaedter et al., 2004). Conversely, patients with hippocampal dysfunction resulting from disorders acquired during adulthood, e.g., global cerebral hypoxia or encephalitis, mostly suffer from bilateral lesions. Behavioral deficits in these patients are thus likely to be the sum of both dysfunctional MTLs, rendering an investigation of possible differential contributions of the right and left hippocampal formation to associative memory difficult. At this stage, it is therefore unclear whether the relative specialization observed in our patients applies to the right hippocampal formation only or to the hippocampal system as a whole. Inferences from our patients' deficits on function in the normal brain are therefore limited to the right hippocampal formation.

Although the impairment in the color-location condition was substantial at 5,000-ms delay, patients performed still above chance level, indicating significant residual processing capacities for visuo-spatial associative short-term memory. Integrity of posterior hippocampal regions ipsilateral to the lesions is unlikely to account for this fact, as damage to the entorhinal cortex was almost complete in our patients. Because most of the communication between the hippocampus and association cortices within and remote from the MTL passes through the entorhinal cortex (Suzuki and Amaral, 1994b) it is probable that intact hippocampal regions posterior to the surgical resection were largely disconnected from these areas (Corkin et al., 1997). The observation of significant visuo-spatial memory functions of the left MTL (Owen et al., 1995, 1996; Kessels et al., 2004; Glikmann-Johnston et al., 2008) may therefore explain the incomplete impairment observed in our patients. Alternatively, pre- or postsurgical processes of reorganisation may have attenuated our patients' deficits. However, as outlined above, pre-surgical reorganisation of memory functions has been reported with disorders such as hippocampal sclerosis, but not with benign brain tumors, such as those of our patients (e.g., Hermann et al., 1992; Seidenberg et al., 1998; Martin et al., 2002; Braun et al., 2008). Pathological changes of regions outside the MTL appear to be associated to early onset of epilepsy and long disease duration, but have not been reported on a time scale of 3.5 yrs following diagnosis of epilepsy (Liu et al., 2002). Lastly, in adults, significant postsurgical recovery of visuo-spatial memory functions is unlikely (Gleissner et al., 2005). We are therefore confident that the postsurgical lesions in our patients provide a legitimate and appropriate model of MTL dysfunction that complements traditional approaches with MTL damage resulting from unilateral surgery for hippocampal sclerosis and from more diffuse bilateral disorders such as encephalitis or global cerebral hypoxia (Stark, 2007).

Types of Associative Memory

In preceding studies, the terms "associative" and "relational" have been used to describe quite different relationships between stimuli or stimulus dimensions, such as the temporal order of item presentation (e.g., Konkel et al., 2008), associations between features of an item or item-feature associations (e.g., Olson et al., 2006; Piekema et al., 2006; Staresina and Davachi, 2008), item-context associations (e.g., Staresina and Davachi, 2008), social relationships (e.g., Kumaran and Maguire, 2005) or spatial and nonspatial associations between items (e.g., Kroll et al., 1996; Giovanello et al., 2003; Turriziani et al., 2004; Kumaran and Maguire, 2005; Hannula et al., 2006; Hannula and Ranganath, 2008). Evidence accumulates that the neural bases of these various types of associations may differ (see Mayes et al., 2007 for review). Like in our preceding studies (Braun et al., 2008; Finke et al., 2008), the experiments reported here exclusively tested memory for associations of different stimulus features. Inferences from our results are thus limited to this segment of memory. Our patients' performance differences within this category nevertheless show that the abovementioned classes of associations do not satisfactorily capture the factors that decide whether or not the affected MTL subregions contribute to memory in our three association conditions. A less descriptive and more fundamental approach to functionally separate different types of associations suggests a classification based on the degree of unitization of the to-be-remembered stimulus material, i.e., the likelihood that a certain stimulus is perceived and represented as a single item (e.g., a face or a colored shape) or as a combination of distinct items (e.g., a face-house pair or spatial relationships between landmarks) (Mayes et al., 2007). However, there is no valid reason to believe that the exceedingly simple color-location, color-shape and color-letter associations of our experiments differ in their degree of unitization. We therefore believe that it was the type of to-be-associated material itself that determined involvement of the affected MTL subregions in its memory.

Visuo-Spatial Associative Memory and the MTL

Among the human lesion studies of the MTL that have investigated associative memory, those that used visuo-spatial material have invariably revealed performance deficits (e.g., Smith and Milner, 1981, 1989; Owen et al., 1995, 1996; Feigenbaum et al., 1996; Abrahams et al., 1997; Varga-Khadem et al., 1997; Bohbot et al., 1998; Henke et al., 1999b; Spiers et al., 2001; Astur et al., 2002; Stepankova et al., 2004; Crane and Milner, 2005; Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007; Braun et al., 2008; Finke et al., 2008). Nevertheless, systematic comparisons of memory for spatial and nonspatial associations have only rarely been carried out. In an influential study of three subjects with hippocampal damage secondary to global cerebral hypoxia during infancy, impaired learning both of object-place and voice-face associations was found, whereas memory for face-face associations or nonword associations was unimpaired (Vargha -Khadem et al., 1997). In a recent study investigating visuo-spatial memory in patients suffering from amnesic syndromes secondary to global cerebral hypoxia sustained during adulthood, both deficits in memory of the spatial relations between elements of visual scenes and in memory of nonspatial face-scene relations were observed (Hannula et al., 2006). By contrast, in a longtitudinal study of a case of bilateral hippocampal damage following carbon monoxide poisoning, rapid recovery of nonspatial associative learning with persistent deficits in spatial associative memory was found (Henke et al., 1999b). Our findings are in good agreement with these latter results by suggesting that it may be the spatial component in the associative stimulus material that critically determines whether the hippocampal formation, at least in the right hemisphere, contributes to performance or not. This interpretation is corroborated by results from fMRI in normal subjects performing spatial and nonspatial associative delayed match-to sample tasks where hippocampal activation was exclusively observed in conditions requiring maintenance of feature combinations that include spatial information (Piekema et al., 2006). Although it is possible that the processes involved in

memory of the simple visuo-spatial associations in these and our experiments partly differ from those involved in memory of more complex associations of multiple visual and spatial items (e.g., in Smith and Milner, 1981, 1989; Crane and Milner, 2005; Kumaran and Maguire, 2005; Hannula et al., 2006; Hartley et al., 2007), our findings show that involvement of the affected MTL regions in associative memory is not limited to associations between complex and distinct items from different domains (e.g., between an object and a visual scene) but rather extends to simple intraitem associations as well (e.g., to a color in a certain location), as long as these associations involve spatial information.

There are however alternative explanations for our findings. Spatial stimuli in our experiments and other studies are necessarily relative, i.e., are encoded relative to each other, the environment, the subjects' retina etc. (Colby, 1998; Banta Lavenex and Lavenex, 2009). This is a major difference to the shapes and letters of our experiments, whose representation does not depend on a similar amount of relative information. Despite evidence from fMRI experiments of increasing hippocampal activation with increasing maintenance of nonspatial associative information (Staresina and Davachi, 2008), we deem it unlikely that the absolute relational content of the stimulus material accounts for the performance differences in our associative conditions. If this factor had been decisive, we would have expected significant deficits in the spatial nonassociative condition too. It appears at least difficult to conceive why the relational content of a stimulus consisting of two colored squares should be higher compared to a stimulus consisting of six gray squares in distinct locations. We thus infer that it was indeed the fact that memory of colors and square locations was required for successful performance in the color-location condition, which yielded the performance deficit in our patients.

Associative vs. Allocentric Memory and the MTL

Although the obvious color- and location-dependency of our patients' deficit appears to suggest an involvement of the affected MTL subregions in associative intraitem memory across spatial and visual domains, there is an important alternative account for our findings. It should be kept in mind, that our spatial stimuli are probably encoded in multiple body-related (i.e., egocentric) and body-independent (i.e., allocentric) spatial-relational coordinate frames (Colby, 1998; Banta Lavenex and Lavenex, 2009). This does not necessarily mean that these coordinate frames and their neural substrates are all pivotal for successful performance in the spatial nonassociative condition. Subjects may have benefited from a 'Gestalt' strategy to solve the nonassociative spatial task, where the sample stimulus configuration is mentally represented as a single entity, even in stimulus arrays with a random arrangement of items. Such a strategy may be less efficient in the color-location condition where the subject is forced to encode multiple spatially distinct items. In this condition, an action-oriented egocentric spatial representation of multiple items may be beyond the capacity of the extrahippocampal regions involved in spatial cognition and may compel the subject to use an allocentric, hippocampus-dependent strategy. It has been claimed recently that lack of control for egocentric strategies may have obscured significant spatial memory deficits in primate models of hippocampal dysfunction (Banta Lavenex and Lavenex, 2009). It appears possible that this partly applies to the observed performance differences between spatial associative and nonassociative conditions in our experiments and in some preceding human lesion studies of visuo-spatial associative memory (e.g., Owen et al., 1995, 1996; Olson et al., 2006; Braun et al., 2008; Finke et al., 2008). In this case, it would not be the association between spatial and visual information that determines involvement of the hippocampal formation, but rather the association between the stimuli and their environment that becomes relevant in conditions that preclude the successful use of nonallocentric strategies.

CONCLUSION

Taken together, the findings in our patients with circumscribed lesions of the right MTL suggest that the right hippocampal formation does not equally support all types of visual associative memory, but rather has a bias for processing of associations involving spatial information. Further testing of spatial and nonspatial associations in larger patient samples with unilateral diseases of the MTL that are acquired during adulthood will have to clarify whether this material-specificity is valid for the hippocampal system as a whole, or whether it is paralleled by a complimentary specialization of the left hippocampal formation. Furthermore, it remains to be determined whether the core deficit behind the memory impairments seen with more complex visuo-spatial material is deficient processing of associations between spatial information and information from nonspatial domains (e.g., the colors of our experiments) or impaired processing of spatial relations per se. The latter account would be consistent with the cognitive map theory of hippocampal function (O'Keefe and Nadel, 1978; Burgess et al., 2002) and recent monkey studies suggesting a central role of the primate hippocampus for allocentric spatial processing (Banta Lavenex and Lavenex, 2009). Experiments in humans with focal disorders of the MTL, requiring maintenance of observer-independent spatial relations rather than objects in locations, may ultimately clarify this issue.

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